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Report of the Federal Panel on Formaldehyde*

The Federal Panel on Formaldehyde concluded that definitive experiments exist which demonstrate the mutagenicity and carcinogenicity of formaldehyde under laboratory conditions. Formaldehyde induces both gene mutations and chromosomal aberrations in a variety of test systems. Inhalation of formaldehyde causes cancer of the nose in rats. The concentrations of formaldehyde in inhaled air that caused nasal cancer in Fisher 344 rats are within the same order of magnitude as those to which humans may be exposed. The data presently available do not permit a direct assessment of the carcinogenicity of formaldehyde to man. Epidemiologic studies on exposed human populations are in progress and may further clarify the situation. Other experimental and human studies on toxic effects such as teratogenicity and reproductive disorders are as yet inadequate for a health risk assessment.

The CIIT 24 month study on animal carcinogenicity has not yet been completely evaluated. Additional data are expected on the effects of prolonged exposure to lower doses of formaldehyde and on the possible carcinogenicity of formaldehyde in the mouse. The panel recommends that, for a comprehensive health risk assessment, further experiments be conducted on the effects of other modes of exposure (ingestion and skin penetration), the effects in humans, and on the pharmacokinetics of formaldehyde in man and animals and the possible role for formaldehyde in reproductive and chronic respiratory disorders.

It is the conclusion of the panel that formaldehyde should be presumed to pose a carcinogenic risk to humans.

Introduction

The first evidence that formaldehyde might represent a carcinogenic risk for man was obtained in October 1979 from an ongoing animal experiment conducted by Battelle Columbus Laboratories for the Chemical Industry Institute of Toxicology (CIIT) (*1*). The preliminary results were reviewed by Federal Government scientists, who concurred with the CIIT conclusions. As the experiment progressed and more data became available, the need for a full review of the potential health risks to humans from chronic exposure to formaldehyde became evident.

To accomplish this review, a panel of scientists from within the Federal Government was formed in April, 1980, under the auspices of the National Toxicology Program and coordinated by the Consumer Product Safety Commission. The panel members reviewed and evaluated the available published and unpublished information on the adverse health effects from repeated exposure to formaldehyde. Acute toxic effects and hypersensitivity were not considered, since they had recently been assessed by the Committee on Toxicology of the National Academy of Sciences (*2*).

Nearly seven billion pounds of formaldehyde are produced each year in the United States (*3*), most in the manufacture of urea-, phenol-, acetal-, and melamine-formaldehyde resins. The remainder is

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used to make other industrial chemicals, agriculture products, leather products, to preserve cosmetics, and to prepare vaccines, drugs, fumigants, and disinfectants. The formaldehyde-based resins are used as adhesives in the manufacture of particle board, veneers, and plywood, and in the production of insulating materials, plastics, protective coatings, textiles, paper, and rubber products.

Under certain conditions, formaldehyde may be released from some of these products, creating the potential for human exposure to the chemical. Its presence in building materials, such as insulation, particle board, and plywood, as well as in other products, has resulted in complaints to the federal regulatory agencies. For example, the Consumer Product Safety Commission (CPSC) has received a number of complaints from consumers concerning adverse health effects associated with the release of formaldehyde gas from urea-formaldehyde foam insulation (*4*). Consumers have also expressed concern that the high concentrations of formaldehyde within their mobile homes may be unhealthy (*5*). Complaints such as these arise because formaldehyde causes irritation of the eyes, nose, throat, and skin, persistent cough, shortness of breath, nausea, headaches, and dizziness. Similar symptoms have been reported by workers who were exposed to formaldehyde resins that are used in the wood, textile, rubber and leather industries.

In October 1979, federal regulatory and research agencies became greatly concerned about the exposure of humans to formaldehyde when representatives of the Formaldehyde Institute reported preliminary findings from a carcinogenicity study showing that rats exposed to 15 ppm of formaldehyde developed squamous cell carcinoma of the nose (*1*). This concern was reinforced in January, 1980, when representatives of the Interagency Regulatory Liaison Group (IRLG) reviewed the carcinogenicity data in detail (*6*). As a result, CPSC, in cooperation with the IRLG agencies, convened a panel of scientists from eight federal agencies under the auspices of the National Toxicology Program to review health data related to formaldehyde. As part of this review, the panel members were asked to consider the following questions (*7*):

- Is there evidence indicating that formaldehyde may be tumorigenic/carcinogenic at doses other than 15 ppm in the CIIT study?
- Are there confounding factors in the CIIT study such as the irritating properties of formaldehyde, viral infection, special susceptibility of the rat to irritants, or protocol defects? If so, what are the relative merits of these factors?
- What conclusions can be drawn from the tumorigenic/carcinogenic results in the CIIT study?
- What is the applicability of the conclusions drawn in the CIIT study to the human situation?
- What is the relation of animal data from other irritant carcinogens to the human situation?
- How do other formaldehyde studies in animals and epidemiological studies affect conclusions about the human carcinogenicity of formaldehyde?
- Do short-term mutagenicity data support findings of carcinogenicity?
- What conclusions can be reached concerning the potential human carcinogenicity of formaldehyde?
- Are there additional data needed?
- Are these findings relevant to exposure from other routes?
- Is there evidence that formaldehyde is teratogenic or causes reproductive effects?

To address these questions the panel evaluated the published literature and available data from ongoing studies. This report is the result of the panel's review.

Chemistry and Metabolism

Chemistry

Formaldehyde, a one-carbon compound with the formula HCHO, has a molecular weight of 30.3 and a boiling point of 19°C. In the gaseous state formaldehyde is a highly reactive chemical with a characteristic pungent odor. It is readily soluble in nonpolar solvents such as chloroform, ether, or toluene but undergoes solvation in polar solvents such as water or methanol. Synthesis of formaldehyde is accomplished typically by the oxidation of methanol in the presence of a copper or silver catalyst.

The common commercial form of formaldehyde (formalin) contains 37–50% formaldehyde in water by weight and is stabilized against polymerization by the addition of 1–15% methanol. Formaldehyde is also commercially available as a solid linear polymer containing 91–95% formaldehyde and 5–9% water (paraformaldehyde or polyoxymethylene) or as a cyclic polymer (trioxane or trioxymethylene). Trioxane, unlike polyoxymethylene, does not readily undergo depolymerization under most conditions.

Formaldehyde undergoes the following chemical reactions in biological systems (*8*):

Hydration in the presence of water:

$$HCHO + H_2O \longrightarrow CH_2(OH)_2 \quad (1)$$

Reaction with the active hydrogen of ammonia, amines, or amides:

$$RNH_2 + HCHO \longrightarrow RNHCH_2OH \quad (2a)$$

$$RNHCH_2OH + RNH_2 \longrightarrow RNHCH_2NHR + H_2O \quad (2b)$$

$$RCONH_2 + HCHO \longrightarrow RCONHCH_2OH \quad (3a)$$

$$RCONHCH_2OH + RCONH_2 \longrightarrow RCONHCH_2NHOCR + H_2O \quad (3b)$$

These reactions are of particular concern because of the ubiquity of nitrogen compounds (DNA, RNA, proteins, amino acids, etc.) in all biological systems. The reaction with purines and other amines produces an intermediate methylol product which is labile. The reaction product with a second amine moiety is stable.

Reaction with other compounds having active hydrogens such as thiols, nitroalkanes, hydrogen cyanide, and phenol:

$$HCHO + HSCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH \longrightarrow H_2C\underset{\displaystyle OH}{\underset{|}{S}}CH\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH \quad (4)$$

Condensation with HCl (and possibly other inorganic chlorides) in the presence of water to form bis(chloromethyl) ether:

$$2HCHO + 2HCl \longrightarrow ClCH_2OCH_2Cl + H_2O \quad (5)$$

Metabolism

Formaldehyde can enter the body through inhalation, ingestion or dermal absorption. Absorption of formaldehyde through the upper respiratory tract in dogs has been estimated to exceed 95% of the inhaled dose (*9*). Following oral exposure of dogs to formaldehyde, formate levels in blood increased rapidly indicating rapid uptake and metabolism (*10*). Dermal absorption has also been demonstrated (*11*) but does not appear to be significant in comparison to inhalation or ingestion.

Formaldehyde that enters the body appears to be converted rapidly to formate (*10, 12*) or to combine with tissue constituents by the reactions described above. The conversion of formaldehyde to formate occurs following intravenous (IV) infusion, subcutaneous injection, gastric intubation, or inhalation. Studies using IV infusion of 0.2*M* formaldehyde into dogs have shown that only a small amount of formaldehyde appears in the plasma during exposure (*10*). This becomes undetectable within 1 hr after cessation of infusion. The peak formate concentration following formaldehyde infusion was the same as when formate (0.2*M*) itself was infused. The plasma halflife for formate (between 80 and 90 min) was also similar. Formaldehyde could not be detected after oral administration of 0.2*M* formaldehyde in the same study while formate increased rapidly in the plasma with a halflife of 81.5 min.

Similar experiments on cynomolgus monkeys, in which 0.2*M* formaldehyde was infused IV, likewise showed no accumulation of formaldehyde in blood (*12*). The blood halflife was estimated to be 1.5 min. Similar halflives for blood formaldehyde have been observed in rats, guinea pigs, rabbits and cats (*13*). In a somewhat different experiment, McMartin et al. (*14*) administered ^{14}C-methanol by gastric intubation. Again, formaldehyde could not be detected although formate levels increased rapidly. A study in which humans were exposed to formaldehyde gas (0.78 mg/m^3) for 3 hr also demonstrated a rapid rise in blood and urine formate levels (*15*).

The rapid conversion of formaldehyde to formate occurred in many tissues in the various species examined, including human erythrocytes (*10*), liver and brain; sheep liver; rat brain, kidney and muscle; rabbit brain; and bovine brain and adrenals (*16*). The enzymes involved have been studied by Strittmatter and Ball (*17*) as well as by Uotila and Koivusalo (*16*). The oxidation is initiated by formation of *S*-formyl glutathione which is then oxidized by NAD and finally cleaved by a thiol esterase, releasing formic acid and glutathione. Formaldehyde has also been reported to be oxidized to formic acid by a nonspecific aldehyde dehydrogenase and by the tetrahydrofolic acid pathway (*18*).

Additional studies (*19*) have shown that following subcutaneous administration of ^{14}C-formaldehyde to rats, approximately 81% of the radioactivity appeared as CO_2. A small amount of the radioactivity was found in choline. Almost 60% of a subcutaneous dose of ^{14}C-formate similarly appeared as ^{14}C-CO_2, with small amounts of radioactivity in choline. Neely (*20*) administered formaldehyde intraperitoneally (IP) to rats and found that 82% of radiolabel was recovered as CO_2 and 13-14% as urinary methionine, serine and a cysteine adduct. At lower doses, only methionine was labeled. The author postulated that CO_2 was derived from serine (formed from glycine and N^5, N^{10}-methylene tetrahydrofolate) by deamination to pyruvate and oxidation in the Krebs cycle. The formation of methionine from ^{14}C-formaldehyde and homocysteine had previously been demonstrated by Berg (*21*). Formation of methionine would also account for the labeled choline observed by DuVigneaud et al. (*19*)

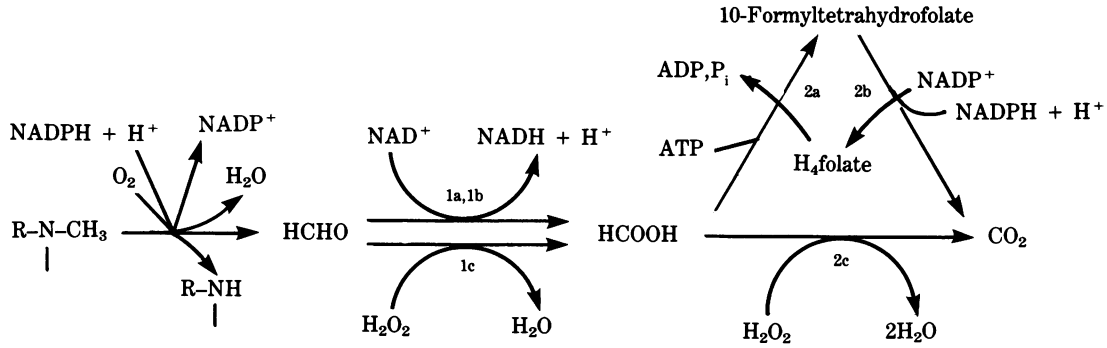

FIGURE 1. Simplified reaction sequence from drug N-demethylation (cytochrome-P-450-dependent monooxygenase) to formaldehyde, formate, and CO_2 production. Reactions are: 1a, formaldehyde dehydrogenase (GSH); 1b, aldehyde dehydrogenase; 1c, catalase (peroxidatic mode); 2a, 10-formyltetrahydrofolate synthetase; 2b, 10-formyltetrahydrofolate dehydrogenase; 2c, catalase (peroxidatic mode).

via methylation of phosphatidyl ethanolamine. More recent work by Pruett et al. (*22*) has demonstrated the incorporation of ^{14}C-formaldehyde into the nucleic acid and protein fractions of WI 38 human diploid fibroblasts. Most of the radiolabel was found in RNA with lesser amounts in DNA and protein. The purine bases of both DNA and RNA were most heavily labeled.

In addition to the serine pathway to CO_2 postulated above (*20*), two other pathways have been identified. These are shown in Figure 1 from Waydhas et al. (*23*).

Waydhas et al. (*23*), McMartin et al. (*14*) and Palese and Tephly (*24*) have demonstrated that the catalase reaction (Fig. 1) is not of major importance and that the primary pathway to CO_2 from formate occurs via the tetrahydrofolic acid pathway. This has been demonstrated in rat liver perfusates (*23*), monkeys (*14*) and rats (*24*). Since the tetrahydrofolic acid pathway (Fig. 2), from Kitchens et al. (*2*), can

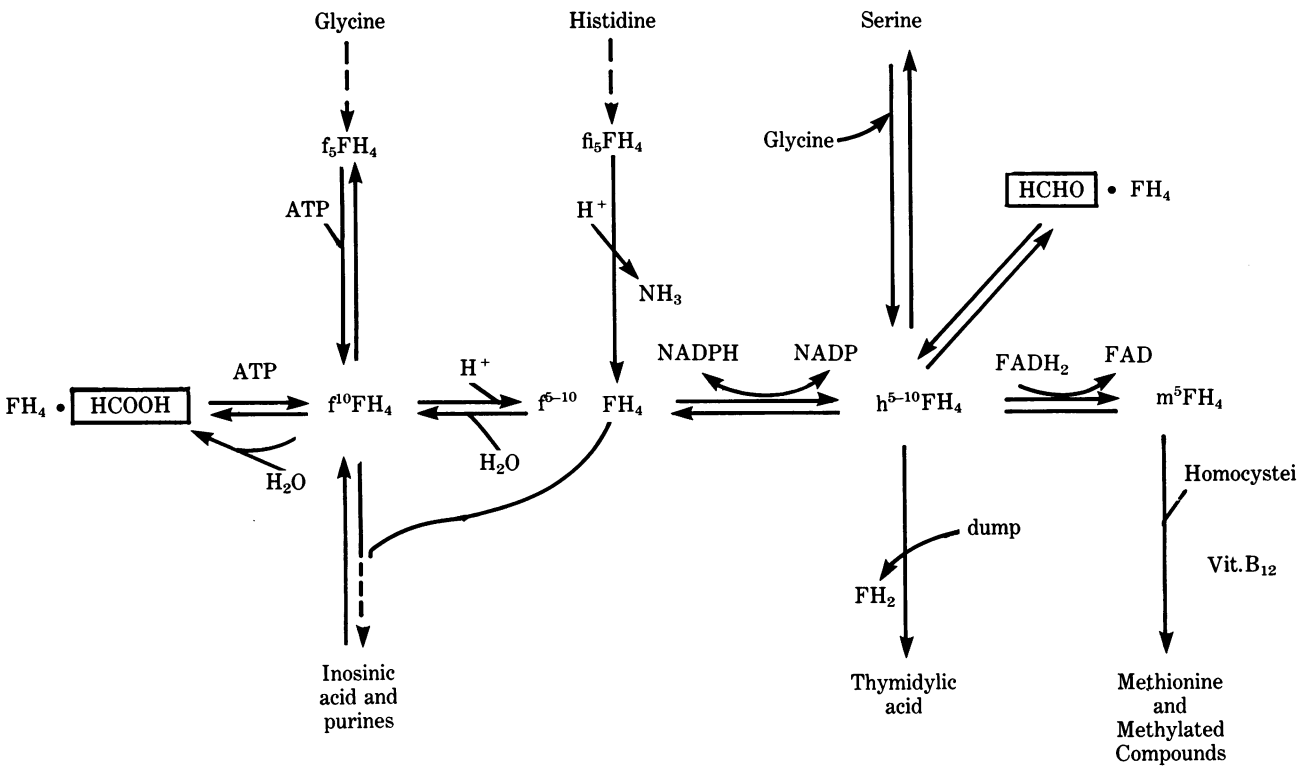

FIGURE 2. Sources of formate. FH_4 = tetrahydrofolic acid; $f^{10}FH_4$ = N^{10} formyltetrahydrofolic acid; f^5FH_4 = N^5 formyltetrahydrofolic acid; $f^{5-10}FH_4$ = N^5 – N^{10} methylnyltetrahydrofolic acid; fi^5FH_4 = N^5 formininotetrahydrofolic acid; $h^{5-10}FH_4$ = N^{10} methylene-tetrahydrofolic acid.

lead to the transfer of the carbon from formate to a number of other compounds (including serine), it is not clear that the 10-formyltetrahydrofolate dehydrogenase reaction (Fig. 1) is the only reaction of importance for CO_2 production in this pathway.

The sources of formate in Figure 2 include the degradation of amino acids such as histidine and tryptophan, and possibly serine and glycine as well. Formaldehyde or formate can also result from *N*-demethylation of drugs such as aminopyrine or ethylmorphine (*23*, *25*) or the metabolism of dihalomethanes (*26*).

Formaldehyde can be formed in mammalian tissues (pig brain and rat kidney) by enzymatic hydrolysis of 5-methyl tetrahydrofolate, in a reaction that appears to require the presence of biogenic amines. The reaction between the amine and formaldehyde is nonenzymatic and leads to the formation of various alkaloids (*27*). A similar reaction involving N^5, N^{10}-methylene tetrahydrofolate is found in human lymphocytes, brain, kidney, and platelets (*28*); it also apparently requires an amine acceptor. Formaldehyde can additionally result from the action of mixed function oxidases on the *N*-methyl groups of various xenobiotics (*29*). The authors report, however, that the rate of oxidation of formaldehyde to formate is higher than the rate of formation of formaldehyde in the above reaction.

Finally, whereas the conversion of formaldehyde to CO_2 occurs in a similar manner in the different species studied, the relative importance of each reaction differs among species and tissues. Thus, the rat is able to convert formate to CO_2 at more than twice the rate of monkeys (or man) and, as a result, has lower blood formate levels (*14*) and does not excrete formate in the urine (*20*). Man additionally possesses 50% more hepatic dehydrogenase than do rats (*30*). With regard to tissue differences, Den Engelse et al. (*31*) have shown that mouse (C3Hf/A) and hamster (Syrian Golden) lungs do not convert formate to CO_2 as efficiently as liver tissue does.

In summary, free formaldehyde is not usually found in plasma or other body tissues in measurable quantities, such endogenous formaldehyde as is produced may be reasonably presumed to be metabolized rapidly to formate or to enter the one carbon pool. When exogenous exposure does occur, formaldehyde is likewise rapidly metabolized to formate and excreted, converted to CO_2 and/or incorporated into other molecules. The same paths seem to occur in all mammalian species examined to date, but reaction rates differ among various species and tissues. Neither the ratio of metabolic deactivation, to tissue or small molecule binding, nor the effect of route of exposure on this ratio is known at this time. Thus, although Egle's work (*9*) suggests that the respiratory tract is the primary area at risk for tumor development, other body sites cannot be ruled out.

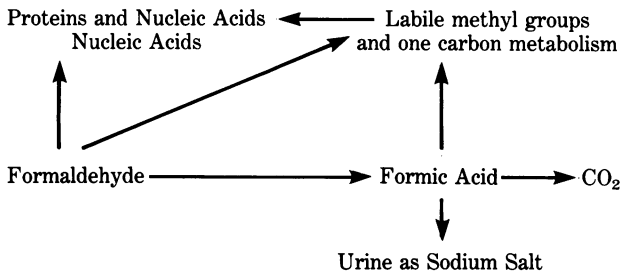

FIGURE 3. Overall metabolism of formaldehyde.

The overall metabolism of formaldehyde is summarized in Figure 3 (adapted from Kitchens et al.) (*8*).

As can be seen from Figure 3, formaldehyde is more chemically active than any of its direct metabolites and would therefore appear to be the chemical substance of most concern for carcinogenicity. The possibility exists, however, as proposed by Poverenny et al. (*32*), that the actual carcinogenic agent may be an amino acid (or other) adduct.

Teratology and Reproduction

Reproduction and Teratology Studies in Animals

The effects of formaldehyde or hexamethylenetetramine (HMT) on teratology and reproduction in laboratory animals have been studied using four methods of administration: inhalation, oral gavage, dietary, or in drinking water. Because the method of administration might have affected the results, the studies are presented chronologically for each method. Hexamethylenetetramine (HMT), an antimicrobial food additive, degrades to formaldehyde and ammonia in an acid medium or in the presence of protein, as in the digestive tract (*33*).

Inhalation Studies. Gofmekler and his colleagues studied the teratogenic and toxic effects of formaldehyde in 36 female rats (12 per group) exposed to 0, 0.012 or 1.0 mg/m^3 from 10 to 14 days before impregnation through gestation. Three male rats per dose level were also exposed for 6-10 days before they were mated.

Gofmekler (*34*) reported the effect of formaldehyde on fertility, fetal weights and organ weights. In both treated groups, formaldehyde caused a 14-15% increase in the length of gestation; it also

increased the average body weight of the offspring and their heart, adrenal, and kidney weights. These changes might have resulted from the extended gestation time. In contrast, the liver and lungs from pups in the treated groups weighed less than those of the control pups. Although Gofmekler stated that there was a decrease in the litter size, his data suggest that this may not be accurate. Our calculations, based on data in Gofmekler's article, show that groups exposed to 0.012 and 1.0 mg/m^3 of formaldehyde had average litter sizes of 19.6 and 17.3 pups, respectively, as compared to the control value of 11.2. These calculations assume that all females in each group became pregnant. Gofmekler stated that some females in each group did not become pregnant, but did not report the details. This implies that several dams produced over 20 pups each.

Gofmekler, Pushkina and Klevtsova (*35*) reported data related to changes in the developing embryo. Identical data were reported by Pushkina, Gofmekler, and Klevtsova (*36*). They measured ascorbic acid in whole embryo, placenta, maternal liver and fetal liver; "nucleic acids" (apparently RNA) in maternal liver, fetal brain and fetal liver; and DNA in maternal and fetal liver. Significant decreases in ascorbic acid concentrations occurred in the whole embryo and in the maternal liver at both dose levels. A significant increase in ascorbic acid concentration in liver occurred in offspring from dams exposed to 0.012 mg/m^3. RNA concentrations in maternal livers were greater at both dose levels than they were in controls. RNA concentrations of fetal brain were similar in control and treated groups. DNA content was significantly lower in maternal and fetal liver in both treated groups than in control animals. The authors concluded that formaldehyde "significantly inhibited the synthesis of nucleic acids." This conclusion is not, however, supported by the data in the article.

Gofmekler and Bonashevskaya (*37*) reported the data related to histopathological changes in the liver and kidneys of fetuses from dams exposed to formaldehyde. The hepatic changes included an increased proliferation of epithelial cells in the bile duct and segmented forms in the hepatic sinusoids. The kidney changes included renal epithelial cells with polymorphic nuclei, casts in the lumina of some tubules, and functional alterations in the renal tubule apparatus. Exposure to 1.0 mg/m^3 of formaldehyde also caused a decrease in myocardial glycogen, an involution of the thymic lymphoid tissue and disintegration of lymphocytes. Histologically, the testes of adult males exposed to formaldehyde were similar to those of the controls.

From macroscopic evaluation it was reported that formaldehyde inhalation by pregnant dams did not affect embryonic or fetal development.

Sheveleva (*38*) studied the teratogenic potential of formaldehyde in pregnant albino rats. The rats were exposed to 0.005, 0.0005 or 0 mg/l of formaldehyde for 4 hr each day on days 1-19 of gestation. Fifteen females per group were killed on day 20, while six were kept to obtain progeny. On day 17 of pregnancy, body weight, spontaneous mobility, rectal temperature and hemoglobin, leukocyte, and erythrocyte concentrations were measured. On day 20, corpora lutea, implantation sites, pre- and postimplantation deaths, and living fetuses were counted. The sizes and weights of living fetuses were determined.

Dams exposed to 0.005 mg/l of formaldehyde exhibited decreased neuromuscular excitability, spontaneous mobility, rectal temperature, and hemoglobin concentration. Exposure to 0.0005 mg/l only caused a slight increase in lymphocytes.

At sacrifice on day 20, the number of preimplantation deaths was higher in both groups exposed to formaldehyde than it was in the controls. Interestingly, the number of live fetuses was approximately the same in all groups. No external malformations were observed in the offspring.

Six dams from each group delivered offspring on day 22; all progeny appeared to be normal at birth. At one month postpartum, the female offspring from control dams were larger than the female offspring from treated dams. For male progeny, the opposite was true. At one month, the spontaneous mobility of progeny from treated dams was less than that of control progeny. By two months, the hemoglobin and leukocyte concentrations were decreased in progeny of dosed dams but not in a dose-related manner.

Guseva (*39*) studied the gonadotropic effects of formaldehyde by measuring testicular nucleic acid content in rats. During a 6 month treatment period, 3 groups of male rats were subjected to a combined action of formaldehyde orally (in drinking water) and by inhalation. Group 1 received formaldehyde at a concentration of 0.1 mg/l in drinking water and by inhalation at a level of 0.5 mg/m^3. Group 2 received formaldehyde at a concentration of 0.01 mg/l and by inhalation at a level of 0.25 mg/m^3. Group 3 received formaldehyde at a concentration of 0.005 mg/l and by inhalation at a level of 0.12 mg/m^3. Group 4 served as untreated controls. Treatment in the drinking water was continuous and simultaneous exposure to formaldehyde by both routes occurred five times per week for 4 hr each time. Reproductive function was evaluated by pairing each treated male with two virgin untreated females. Although the number of males was not

specified, the use of six females per group implies the use of three males in each group. On day 20, an unspecified number of pregnant females were killed and their offspring were removed and examined. Guseva failed to mention the results of the examination of the fetuses. The remaining dams were allowed to produce offspring. The number and weight of newborn rats were recorded. Observations of their subsequent development extended over one month. The time of eye opening and other developmental indices were recorded for the offspring of males in groups 1 and 3 only.

The capacity of the treated males to produce offspring was not diminished. There was no effect on the weight of the fetuses or the size of the litters. The offspring were morphologically normal at birth and developed normally thereafter. Gonadotrophin levels were not significantly different between males in the control group and those in the treatment groups. However, the amount of nucleic acid in the testes of males of groups 1 and 2 was significantly less than the amount in the testes of the controls.

Sanotskii et al. (*40*) studied the effects of formaldehyde on reproduction in an unspecified strain and number of albino rats. They exposed groups of pregnant and nonpregnant rats to 0, 0.4 or 6.0 mg/m^3 of formaldehyde for 4 hr/day for 20 days. Evaluations were made of body weight, nervous system function, renal function, hepatic function, and biliary levels of cholic acid. Blood parameters, oxygen uptake, and rate of respiration were measured.

Nonpregnant animals were more susceptible to the effects of formaldehyde than were pregnant animals. Formaldehyde at 6.0 mg/m^3 resulted in altered renal function as shown by decreases in daily diuresis and urinary chlorides and an increase in urinary protein concentration. The increase in urinary protein may have reflected decreased urinary output. Altered hepatic function was manifested by a decrease in urinary excretion of hippuric acid. At 6.0 mg/m^3, only blood hemoglobin decreased in the pregnant rats. Exposure to 0.4 mg/m^3 did not produce toxic changes in either pregnant or nonpregnant rats.

All the studies suffered from an unreported or inadequate number of animals treated per dose level. In the teratology studies, detailed results from skeletal and soft-tissue analyses were missing. None of the studies had a sufficient number of dose levels to fulfill current requirements. Even with these deficiencies, there were indications that formaldehyde might affect reproductive potential by altering testicular nucleic acids and by increasing pre-implantation losses.

Dietary Studies. Hurni and Ohder (*41*) studied the effects of formaldehyde on reproduction in the beagle. Groups of 9-11 pregnant bitches were fed dietary levels of 600 or 1250 ppm HMT, or of 125 or 375 ppm formaldehyde, from 4 days after mating to day 56. Eleven control dogs ate unadulterated chow. The bitches were weighed weekly. The pups were weighed at birth and twice weekly thereafter. They were inspected for visible defects immediately after birth and at 8 weeks postpartum. Stillborn pups and those that died before weaning were autopsied and examined for internal and skeletal anomalies.

Neither formaldehyde nor HMT affected the pregnancy rate. Maternal body weights increased normally during pregnancy in all groups. The duration of gestation was not affected by formaldehyde or HMT. Mean litter sizes were within the normal range for all groups. In the group that received 1250 ppm of HMT, there was a greater percentage of stillborn pups than in any other group; this was mainly due to one litter in which 7 of 9 pups were dead. The stillborn pups were not malformed.

During the first month, the pups from bitches given 1250 ppm HMT grew less than normal. The retarded growth coincided with increased mortality. In the same group, the percentage of pups that survived to weaning was lower than it was in the other groups. All the dogs that were observed for up to 9 months exhibited normal behavior, appearance, mobility, and muscular coordination.

Natvig, Andersen and Rasmussen (*42*) studied the effects of HMT fed to Wistar rats. Two groups of 16 male and 16 female rats each were fed a diet containing 0.0 or 0.16% HMT starting at 2 months of age and continuing for three months, when they were mated with group mates. Their offspring were fed the same diet. The offspring were weighed at 7 and 15 weeks, measured for voluntary muscle activity at 6 weeks, and killed when they were 123 days old. Half of them were autopsied.

There were no detectable differences between the test and control groups. The fertility of the treated animals was similar to that of control animals. The offspring from both groups had similar muscular activity, body weights, general health and organ weights.

For the purpose of clarifying the teratogenic potential of formaldehyde, it is unfortunate that in both of these studies the dams were allowed to deliver naturally. Removing all the pups by cesarean section would have permitted detailed examination for anomalies. By allowing the dams to litter, it was possible that the malformed pups were eaten by the mother before being seen by the investigator. Neither report states if an observer was present at all deliveries. Although teratogenic

effects were not noted, HMT appeared to have fetotoxic and postnatal effects in the beagle at 1250 ppm (31 mg/kg). In the rat study, additional dose levels would have been desirable.

Intubation Studies. Marks, Worthy and Staples (*43*) intubated pregnant outbred albino mice on days 6-15 of gestation with 1% aqueous formaldehyde at levels of 0, 74, 148, or 185 mg/kg/day. On day 18, the mice were killed and the offspring examined. All mice were coded in a manner that prevented laboratory personnel from knowing which ones belonged to the control and test groups. Visceral observations were made by the Staples technique and all fetuses were examined for skeletal anomalies.

Formaldehyde was toxic to 22 of 34 pregnant mice at 185 mg/kg. At 74 mg/kg, there was a significant decrease in average weight gain during pregnancy. Formaldehyde treatment, at any dose level, did not result in malformations.

Although formaldehyde caused toxicity in pregnant mice, it was not teratogenic. Because of the methods employed and the number of animals used at each level, this appears to be a valid, reliable, and negative teratogenic study of orally administered formaldehyde.

Drinking Water Studies. Della Porta, Cabral and Parmiani (*44*) conducted several studies on the effects of HMT in rats and published results in a single manuscript.

In the short-term reproduction and toxicity experiment, 12 females and 6 males were given a solution of 1% HMT in the drinking water, beginning at 8 weeks of age. Two weeks later, the animals were mated (2 females: 1 male) and treatment of the females was continued during pregnancy and nursing. Twenty-four males and 24 females were randomly selected from the progeny and treated as above until 20 weeks post partum. Each animal was weighed weekly. At the end of treatment, the animals were sacrificed, their organs were weighed, and histological examinations were conducted. Groups of 12 untreated dams and 48 pups were used as controls.

All treated females and 11 of 12 control females became pregnant and produced 124 and 118 offspring, respectively. The progeny of the treated females were not malformed. The mean body weights of the treated males and females were significantly less than those of controls. These differences lasted up to 9 weeks for males and to 13 weeks for females. After these times, body weights became comparable to the control values. When the offspring were autopsied at 22 weeks, no microscopic or macroscopic lesions were seen. Body weights and organ weights (liver, kidneys, spleen, thymus, pituitary, adrenals and testes) were similar for treated and control groups.

In the second experiment, two females and one male were given a solution of 1% HMT in the drinking water before mating. The treatment of females continued until two litters of 10 rats each had been weaned. Treatment of the F_1 progeny continued until they were 40 weeks of age. To produce an F_2 generation, seven F_1 females were mated with three F_1 males at 26 weeks of age. F_2 animals were mated at 15 weeks of age to produce an F_3 generation. F_1 and F_2 animals were given HMT until the 40th week postpartum; F_3 animals were given HMT to the 20th week. F_1, F_2 and F_3 animals were observed for 130 weeks (2.5 years). All survivors were sacrificed when they reached 3 years of age.

The survival rates of all the generations of offspring were not affected by treatment. Mean body weights, obtained many times during the experiments, showed no significant differences between control and treated groups.

In another study, five adult female rats were bred and treated with 2% HMT in the drinking water until 49 offspring were weaned. The offspring were treated with 2% HMT until they were 50 weeks of age. After treatment, the survivors were observed until 130 weeks of age. Rats (48 males and 48 females) from a previous study served as controls; they were observed until they were 3 years of age. Mean body weights were not significantly different between treated and control animals.

All three studies lacked a sufficient number of animals per dose level and number of dose levels to permit a meaningful evaluation of the potential of HMT to affect reproduction of fetal development. The third study also lacked appropriate concurrent control animals.

Reproduction and Teratology Studies in Humans

Shumilina (*45*) studied the reproductive potential of women who were exposed to formaldehyde. In the study, the menstrual and reproductive functions of 446 women were evaluated in two experimental groups. The first group of 130 women were fabric trim shop finishers. The second group of 316 women were fabric warehouse inspectors. A third group of 200 industrial goods saleswomen who were not exposed to formaldehyde were used as controls. The trim shop finishers worked in atmospheric concentrations of formaldehyde ranging from 1.5 to 4.5 mg/m^3. The warehouse inspectors worked where formaldehyde concentrations varied from 0.3 to 0.7 mg/m^3 in one shop and from 0.05 to 0.1 mg/m^3 in

another shop. All women were given complete medical examinations.

Menstrual disorders were found in 47.5% of the women exposed to formaldehyde as compared to 18.6% of the controls. Dysmenorrhea was found in 24.3% of the finishers as compared to 9.2% of the controls and 20.2% of the inspectors. It occurred more frequently in the 31-40 year-old women (20.7% in the experimental group versus 6.7% in the controls). A cause of the painful menstruation was not found. Hypomenstrual syndrome occurred in 1.2% of the finishers with less than 5 years of potential exposure to formaldehyde, in 47% with 6-10 years of potential exposure, and in 6.8% of cases with more than 10 years of potential exposure. More menstrual disorders were found in workers below 30 years of age (33.4%), but fewer disorders were observed in persons aged 30-40 years (20.8%).

The incidence of inflammatory diseases in the reproductive tract among trim shop finishers was 38.2% and among the warehouse inspectors it was 25.1%. Both of these values were greater than the control value ($p < 0.05$). The percentage of women with exposure to formaldehyde who had primary sterility was 5.2; this value may be compared to 2.5% incidence in the controls. The incidence of secondary sterility was 15.3% in the finishers, as compared to 6.5% in the controls. The high incidence of secondary sterility in exposed women may have been due to previous inflammatory diseases.

The number of term deliveries and artificial abortions did not differ significantly among the groups of workers investigated. Anemia, the most frequent complication of pregnancy, occurred twice as often in women exposed to formaldehyde, as it did in control women. The hazard of intrauterine asphyxiation of the fetus was also encountered twice as often in the exposed women as in the control group. The percentage of children with low birth weights was greater in women exposed to formaldehyde than it was in the control women.

Menstrual disorders were found in women exposed to formaldehyde. Although the number of term births and artificial abortions did not differ among the groups, there were increases in primary and secondary sterility, anemia, and intrauterine asphyxiation of the fetus among women exposed to formaldehyde. Though these data have many limitations, they raise the possibility that formaldehyde may affect human reproductive processes. Additional research is needed to confirm these effects.

Reproduction-Related Studies

Palkovits and Mitro (*46*) studied formalin-induced stress in neonatal rats. They injected one group of newborn Wistar rats with 0.02 ml of 2% formaldehyde IP once on the day of birth. A second group was injected daily for the first 4 days after birth. Control animals were untreated. At 24 hr after the last injections, all neonates were decapitated. The adrenals and hypothalamus were examined microscopically.

In the neonates injected for 4 days, degenerative cellular atrophy occurred in the ventro-medial arcuate of the hypothalamus. Single injections of formaldehyde did not cause degenerative changes but did cause decreased cellular activity in the medial field of the ventromedial nucleus and the arcuate nucleus and an accumulation of granules in the neuronal cytoplasm. In both groups, formaldehyde injections increased nuclear volume in the adrenals. These changes indicate that the hypothalamus of the neonatal rat is sensitive to corticoid feedback induced by formaldehyde administration.

Cohen (*47*) studied the response to formaldehyde injection in fetal rats by measuring ascorbic acid levels in the adrenals. Pregnant female rats were anesthetized with ether and delivered by cesarean section. The first fetus from each litter served as the control. Approximately 6 μl/g of 2% formaldehyde were then injected SC into one or more litter mates. Fetuses were injected with formaldehyde at 18.5, 19.5, 20.5 or 21.5 days of gestation.

Injections of formaldehyde resulted in decreased ascorbic acid levels in the adrenals at 20.5 days of gestation. Injections on other days of gestation did not cause this response in fetuses.

Conner et al. (*48*) studied the effects of formaldehyde injected into the uterus of pregnant rats. They were interested in its potential as a contragestational agent. On day 3 or day 7 after mating, they injected 0.05 ml of formaldehyde (40, 10, 7, 3.5, 2.0, 0.5, 0.05 or 0.0005%) into one uterine horn and 0.09% saline into the other horn (control) of 3-5 pregnant Sprague-Dawley rats/group. All solutions of formaldehyde also contained 12-15% methanol. On day 15, dams were sacrificed, and the number of corpora lutea, viable fetuses, and resorptions were counted.

Injections of 40 and 10% formaldehyde produced maternal toxicity and death. Injections of 7.0 through 0.5% on day 3 terminated most pregnancies. When these concentrations were injected on day 7, most pregnancies continued. The authors concluded that the contragestational properties of formaldehyde were similar to those of other protein denaturing agents, including ethanol, methanol and silver nitrate. Because methanol solutions alone were not tested, contragestational effects of methanol could not be clearly distinguished from those of formaldehyde.

These physiological and endocrine studies are

interesting but their relation to the teratogenic potential of formaldehyde is unclear.

Dominant Lethal Studies

Epstein et al. (*49*) tested formaldehyde for mutagenicity by the use of the modified dominant lethal test. Male ICR/Ha Swiss mice were given a single dose of 16, 20, 32 or 40 mg/kg of formaldehyde IP. After dosing, each male was placed with three females weekly for 3 weeks. Alternatively, male ICR/Ha Swiss mice were given dose levels of 16 or 20 mg/kg IP and placed with three females weekly for 8 weeks. At the dose levels tested, formaldehyde did not produce an increase in early fetal deaths or pre-implantation losses.

Formaldehyde did not appear to affect spermatogenesis or fertility in mice at the dose levels tested in this study.

Recommendations

Teratology. The data are inadequate to demonstrate whether or not formaldehyde is teratogenic. The panel's survey revealed only one well-conducted study and that was done by oral administration in mice (*43*). Recommendations are that teratology studies should be performed in rats and rabbits and that these studies should include the administration of formaldehyde by inhalation.

Animal Reproduction. The study of Della Porta et al. of HMT (*44*) lacked the proper number of animals per group needed to evaluate reproductive and teratogenic effects. Multigeneration studies with a larger number of animals should be conducted to test the effects of formaldehyde on reproduction.

Although the physiological and endocrine studies contribute to an understanding of the reproductive effects of formaldehyde, many questions remain unanswered. Mechanisms of biochemical changes and teratology cannot be elucidated until additional biochemical and pharmacological studies are done including placental transfer studies.

Human Reproduction. Shumilina's study (*45*) revealed several possible effects of formaldehyde on human reproduction, but the study lacks sufficient data to answer the questions it raises. Controlled epidemiological studies should be conducted.

Mutagenicity

In a review of the extensive literature on the genetic toxicology of formaldehyde by Auerbach et al. (*50*), the results of experiments on formaldehyde-treated food in Drosophila are discussed as well as data obtained by exposure of other organisms to vapor or aqueous solutions of formaldehyde and by combination treatments with formaldehyde and other mutagens. Formaldehyde treatment alone gives positive but weak responses in many laboratory organisms; both gene mutations and various types of chromosome aberrations are produced. A brief summary of the genetic effects of formaldehyde has also been published by Cooper (*51*).

Genetic Effects of Exposure

Formaldehyde-Treated Food. The most extensive data (*50*) have resulted from treatment of Drosophila with formaldehyde-food (FF). In the early experiments of Rapoport (*52*) treatment of young larvae resulted in an increase of sex-linked recessive lethals from a control frequency of 0.2% to about 6%. FF produced all types of gene mutations (both point mutations and deletions) and chromosome rearrangements (small duplications and deficiencies to inversions and translocations). These results were independently confirmed by Kaplan (*53*). Slizynska (*54*) compared the structural changes induced by FF with those produced by x-rays. In contrast to 97% translocations or inversions and fewer than 3% small deficiencies or duplications induced by x-rays, only 30% translocations or inversions and 64% small duplications or deficiencies were found among FF-induced changes.

Formaldehyde Vapors. No mutations were produced by exposing Drosophila adults for up to 1 hr or larvae for up to 2 hr to sublethal concentrations of formaldehyde gas (*55*).

Formaldehyde Solutions. Early experiments in *Escherichia coli* B (*56*) showed that formaldehyde is a very weak agent for the production of point mutations from streptomycin-dependence to independence. Injection of formaldehyde solutions into adult Drosophila provided an effective means for inducing sex-linked recessive lethal mutations, but lower frequencies were found than obtained with FF (*57*, *58*).

More recent studies have shown that the ability of formaldehyde to induce forward mutations at specific loci in the *ad*-3 region of Neurospora (by direct treatment at levels producing 75 - 5% survival) increased from a spontaneous frequency of 0.4×10^{-6} to $4 - 6 \times 10^{-6}$ among survivors (*59*). With this assay, gene mutations resulting from both point mutations and multilocus deletions can be detected. Genetic characterization of formaldehyde-induced *ad*-3 mutants is in progress. Formaldehyde was found to induce point mutation by reverse-mutation in both Neurospora (*60*, *61*) and Aspergillus (*62*), but not in Salmonella (*63*, *64*). The National Toxicology Program has reported that, in recent inves-

tigations by three independent laboratories using the Ames test, formaldehyde tested positively in one of four bacterial strains (TA 100) that detects base-pair substitution mutations.

A number of genetic effects have been found in mammalian cells in culture. These include: (1) an 8-10 fold increase in forward mutation frequency at the thymidine kinase (TK) locus in mouse lymphoma cells (*65*); (2) a 1.5–3-fold increase in the frequency of sister chromatid exchanges in Chinese hamster ovary cells and in human lymphocytes in culture (*66*); and (3) induction of unscheduled DNA synthesis in HeLa cells over a dose range of $10^{-6} - 10^{-8}$ *M* (*67*).

Mammalian* in vivo *Studies. No data were found in the literature on the induction of genetic damage in mammals either in somatic cells or germ cells. Epstein et al. (*68*) were unable to detect early fetal deaths induced by formaldehyde injection in an assay for dominant lethality in mice.

Interaction with Other Mutagens. In Drosophila, Sobels (*69*) found that either pre- or post-treatments with formaldehyde almost doubled the frequencies of x-ray-induced sex-linked recessive lethals. In Neurospora, early experiments by Dickey et al. (*70*), Kolmark (*71*), and Kolmark and Westergaard (*72*) showed that formaldehyde by itself is only weakly mutagenic, whereas a mixture of formaldehyde and peroxide gave a much higher effect than could be predicted on the basis of a strictly additive effect of the two agents.

Increased Effects in Repair-Deficient Strains. Nishioka (*73*) compared the lethality and mutagenic damage produced by formaldehyde in *E. coli* strains HCR+ and HCR- and found that, in the latter excision-repair deficient strain, much higher levels of effect were produced. Comparisons of the ability of direct treatment with formaldehyde solutions to induce specific locus mutations in the *ad*-3 region of wild-type and excision-repair deficient, two-component heterokaryons of Neurospora have shown up to a 370-fold higher mutation frequency in the excision-repair deficient strain (*59*). The same is true for excision-repair deficient mutants of *Saccharomyces cerevisiae* (*74*). In addition, more pronounced genetic effects of formaldehyde were found with cell lines of *Xeroderma pigmentosum* as compared with normal human fibroblasts in culture (*75*).

Summary

Formaldehyde produces gene mutations and such chromosome aberrations as deficiencies, duplications, inversions, and translocations; no data are available for the production of aneuploidy. In most experiments, dose-response relationships could only be demonstrated with difficulty or not at all, and all data are consistent with the classification of formaldehyde as a weak mutagen. Formaldehyde has been shown to interact with other mutagens such as x-rays, ultraviolet radiation and hydrogen peroxide, and to at least double the frequencies of mutants expected from treatment with these agents. Formaldehyde effects on both lethality and the induction of mutations in microbes are markedly enhanced in excision-repair deficient strains. No data are available from studies on mammalian systems *in vivo* on genetic effects on germ cells.

Risk Assessment

Since there are no effects reported on mammalian germ cells the genetic risk of exposure to formaldehyde can only be made by extrapolation from experiments with other laboratory organisms. The only genetic data relevant for risk estimation are those for the induction of gene mutations and chromosome aberrations. There are no data on the induction of aneuploidy by nondisjunction or any other mechanism. In this respect, the most extensive data result from experiments with Drosophila on formaldehyde-treated food. It is not known how representative these data are of genetic effects that would be expected from exposures to vapors or solutions. The Drosophila data show that 64% of the transmitted chromosomal effects studied resulted from small duplications or deficiencies, the remainder were due to large inversions and translocations. No data were found which would be useful in determining whether a comparable spectrum of genetic alterations would be found with lower chronic levels of exposure. In conclusion, although heritable genetic damage has been demonstrated, only small increases would be expected from the levels of formaldehyde which might reach the germ cells. The Drosophila data, for example, indicate that sensitivity is limited to effects on males and is restricted to early spermatocytes; whether similar effects can be expected in whole animal systems is unknown.

Recommendations for Future Studies

The genetic effects of formaldehyde in man could be more readily predicted if selected experiments were performed on laboratory animals. Such studies could begin with an experiment using the *in vivo* mammalian spot test to determine whether formaldehyde vapors or solutions would cause gene mutations in somatic cells that affect coat color (*76*). This test has the advantage of requiring exposure and

analysis of progeny from only 30-50 pregnant females. The test is thus relatively inexpensive and has been used to evaluate the mutagenic activity of a wide range of chemical agents.

In the event of a positive result in the mammalian spot test, two additional assays should be applied in mice: (1) the heritable translocation test (*77*) and (2) the morphological specific locus test (*78*). Considerably more work is involved in these two assays but they are useful to determine, respectively, whether heritable chromosome aberrations and gene mutations have been produced. In the presence of a negative spot test it is unlikely that positive results would be found in the latter two tests which detect genetic effects produced in male germ cells.

Carcinogenicity

The literature search revealed only a few studies that were designed for the purpose of testing formaldehyde for carcinogenic activity. Because of limitations in experimental design, many of the reported studies are inconclusive. In this section only those studies will be reviewed which were conducted over a sufficient length of time to permit detection of carcinogenic activity activity of the test chemical. The investigations will be discussed in order of their importance as judged by this panel, starting with the inhalation exposure studies.

Review of Formaldehyde Carcinogenesis Studies

By far the most important carcinogenesis study conducted to date with formaldehyde is the CIIT inhalation study recently reported by Swenberg et al. (*79*). F344 rats and B6C3F$_1$ mice (120 male and 120 female rats or mice per group) were chronically exposed to 2.1, 5.6 and 14.1 ppm of formaldehyde vapors for 6 hr/day, 5 days/week. During the first 18 months of exposure, 2, 2, 8 and 44 rats died in the groups exposed to 0, 2.1, 5.6 and 14.1 ppm of formaldehyde, respectively. Of the 44 rats which died spontaneously in the group exposed to 14.1 ppm, 32 had nasal tumors (28 squamous carcinomas and four squamous papillomas). Many of the rats also showed hyperplastic and metaplastic lesions of the nasal epithelium. Hyperplastic and metaplastic lesions were also detected in rats exposed to 5.6 ppm formaldehyde (14 lesions were found in eight rats), indicating that the nasal epithelium was significantly damaged at this lower level of exposure. At 18 months of exposure, 40 rats were killed in each group. Eight of 40 rats exposed to 14.1 ppm had developed nasal squamous carcinomas. Although no carcinomas of the airways were found in the other groups, one adenomatous polyp was found in one rat of each of the groups exposed to 2.1, 5.6 and 14.1 ppm. In addition, a large number of hyperplastic and metaplastic lesions was detected in the nasal epithelium of these rats, even at formaldehyde concentrations as low as 2.1 ppm. No exposure-related tissue abnormalities were reported at sites other than the nasal cavities and no exposure-related neoplasias were reported in formaldehyde exposed mice, but examination of the animals sacrificed after 24 months of exposure is not complete.*

One complication noticed during the study was a spontaneous outbreak in rats of sialodacryoadenitis. The evidence for this consisted of decreased body weight in all dosed and control rat groups at about the 52nd week of the experiment, followed by prompt recovery of body weight, and histopathological demonstration of typical lesions in lacrimal and salivary glands and in the upper respiratory tissues of dosed and control rats in the 12 month sacrifice groups. Evidence of sialodacryoadenitis was not found in rats sacrificed at 6 or 18 months or in those with unscheduled deaths. Virus isolation, viral antigen demonstration, and serologic tests for antibodies were not attempted in rats or mice.

With regard to formaldehyde in the exposure chamber, a panel of experts reviewed the method of formaldehyde generation and monitoring and "agreed that the Battelle approach to formaldehyde vapor generation was a suitable adaptation of accepted methods and principles and, therefore, was sound and based upon the best available technology. The same type of assessment applied to the chamber air monitoring system, which also combined two well-established procedures" (*81*).

Suggestive evidence for the carcinogenicity of inhaled formaldehyde vapors also comes from a study by Laskin et al. (*82*). One hundred male Sprague-Dawley rats were exposed to a mixture of gaseous formaldehyde (14.7 ppm) and hydrogen chloride (10.6 ppm) for 6 hr/day, 5 days/week for life. Of the exposed rats, 27% developed nasal tumors, of which 25 were squamous carcinomas and

*The Chemical Industry Institute of Toxicology recently reported results up to and including the 24 months sacrifice, as follows: in rats exposed at 14.1 ppm there were 93 animals with squamous cell carcinomas, four with squamous papillomas, three with adenomatous polyps and two with carcinomas of the respiratory epithelium; at 5.6 ppm there were two squamous cell carcinomas, four adenomatous polyps and one carcinoma of the respiratory epithelium; and at 2.1 ppm, five rats had developed adenomatous polyps. Additionally, two mice sacrificed at 24 months were found to have nasal squamous cell carcinomas (*80*).

two were papillomas. No nasal tumors were found in 100 control rats. Both dosed and control rats had pneumonia but the lesions were more severe in dosed rats. The estimated bis(chloromethyl) ether (BCME) level in the exposure chamber (developing as a result of the chemical interaction of formaldehyde and hydrogen chloride) was 1 ppb. This value was computed on the basis of 10 measurements made in the mixing chamber during the course of the study. It is not certain whether the high nasal cancer incidence is a result of the formaldehyde exposure, the (presumed) BCME exposure, or the biological interaction of the two or three components of the gas mixture. Based on their previous studies (*83*), the authors considered the BCME level to be too low to be a significant etiological factor for the nasal cancers observed in this study. They also point to the fact that in rats, BCME caused mostly esthesioneuroepitheliomas rather than squamous carcinomas in the nasal cavities. While the results suggest that formaldehyde (rather than BCME) is the major etiological agent in this experiment, considerable uncertainty remains and other interpretations are possible. The authors' comparison of 20 exposure days at 100 ppb of BCME (*83*) with 500 exposure days at 1 ppb of BCME (*82*) does not, however, resolve the uncertainty of comparing the different factors involved in dose-rate versus total delivered dose in tumor induction.

Three other chronic inhalation studies with formaldehyde designed to investigate possible cocarcinogenic effects of this agent in the upper and lower airways have been reported (*84-86*). Since the nasal tissues were not systematically examined histologically, the value of these studies in assessing the carcinogenicity of formaldehyde is accordingly limited. In spite of these reservations, the studies have some bearing on the problem of formaldehyde carcinogenicity. In the studies conducted at the Oak Ridge National Laboratory (ORNL) by Nettesheim and colleagues (*84*), Syrian Golden hamsters were exposed by intratracheal (ITr) instillation to different doses of benz(a)pyrene (BaP) and by inhalation to various concentrations of formaldehyde (acrolein exposures were carried out in parallel studies). Two types of formaldehyde exposure schedules were used: 10 ppm for 5 hr/day, 5 days/week for life (two groups) and 20 or 50 ppm for 5 hr/day, 1 day/week for 17 weeks (seven groups). In all, nine groups of 88 hamsters each were exposed to formaldehyde (with or without BaP exposures; two groups were exposed to formaldehyde only). Significant in the context of this discussion is that no macroscopically recognizable nasal tumors were observed in hamsters, whereas in the studies with rats by Swenberg et al. (*79*) and by Laskin et al. (*82*), grossly visible tumors developed. Based on extensive histopathological evaluation, there was no evidence for the carcinogenicity or cocarcinogenicity of formaldehyde for the larynx, trachea and lower airways. No neoplasms were found in two sections of nose from each hamster, but the level of sectioning was not rigorously controlled.

In the study reported by Horton et al. (*85*), C3H mice were exposed to coal tar aerosol and/or to formaldehyde at concentrations of 40, 80 and 160 ppm. Exposures were carried out for 1 hr/day, 3 days/week for 35 weeks, except for the 160 ppm group which was exposed only for 4 weeks because of toxicity. Only 15 mice survived to 1 year. There is no mention of histopathological evaluation of nasal tissues, so presumably no grossly visible tumors were observed. Coal tar aerosol exposure resulted in lung tumor formation in five animals (one invasive carcinoma) but formaldehyde exposure did not. No evidence was found for any cocarcinogenic effects of formaldehyde. The major shortcomings of this study for evaluating the carcinogenic activity of formaldehyde are that too few animals survived past one year, the individual exposures were short, most groups were exposed only for 35 weeks, and histopathology was inadequately reported.

A third study (as yet unpublished) has been performed by Dalbey and Nettesheim at the Oak Ridge National Laboratory (*86*). In this study, male Syrian Golden hamsters were exposed to diethylnitrosamine (DEN) subcutaneously (0.5 mg once weekly for 10 weeks) and to inhalation of either nitrogen dioxide (10 ppm) or formaldehyde (30 ppm). Exposures to NO_2 and formaldehyde were made once weekly for 48 hr prior to each DEN injection and were subsequently continued for lifetime after DEN injections were completed. An analysis of tumor data indicated that formaldehyde (but not nitrogen dioxide) might act as a tumor "enhancing agent" in the trachea as measured by multiplicity of tumors. This study was limited because, at the doses used, DEN alone produced tumors in a high proportion of animals.

The carcinogenicity of formaldehyde has also been tested by a variety of other routes of administration including subcutaneous injection (in rats), ingestion (by mice and rats), uterine cervical application (in mice) and application to the buccal mucosa (in rabbits). Because of shortcomings in experimental protocols, none of these studies permits firm conclusions regarding formaldehyde carcinogenicity. Nonetheless, some of the studies give definite clues that formaldehyde may be carcinogenic to a variety of target tissues as well as a variety of animal species (and not only to the nasal epithelium of rats).

The most revealing study in this regard is that by Mueller et al. (*87*), who applied a solution of 3% formalin to the oral mucosa of rabbits, using an "oral tank." Each exposure lasted for 90 min and was repeated five times per week for a period of 10 months. As a result, two out of six rabbits developed grossly visible leukoplakias that, according to the authors, showed histological features of carcinoma *in situ*. Unfortunately, the information given on the histomorphology of the lesions is very scanty. Nevertheless, the reported observations appear to be consistent with the rat inhalation studies, suggesting that formaldehyde is a carcinogen.

Also of considerable significance are the observations reported by Brusick et al. (*88*) concerning the transformation of mouse Balb 3T3 cells *in vitro* by formaldehyde concentrations as low as 0.5 μg/ml culture fluid. At this time, no other pertinent information is available on these studies.

Probably the earliest experiments which suggest that formaldehyde is a carcinogen are those by Watanabe et al. (*89*, *90*), who injected rats (strain unknown) subcutaneously with 0.4% formalin (1 ml/week for 15 months) (*89*) and with 9-40% of hexamethylenetetramine (HMT) (from which formaldehyde is liberated *in vivo*) 1-2 ml per week until tumor development (*90*). In the first study (*89*), four of ten rats developed sarcomas at the site of the injection, and in the second study (*90*), eight out of 20 rats developed tumors, seven sarcomas and one adenoma. There is little doubt that tumors were induced by the subcutaneous injections of both chemicals over many months. It is not certain, however, what the role of the repeated severe injury to the subcutaneous tissue may have been in the induction of the sarcomas even through results with formic acid were negative (*90*).

Several other studies carried out with HMT resulted in negative findings. Brendel (*91*) administered HMT daily by gavage to 15 male and 15 female BD rats (0.4 g/day) for 333 days. No treatment-related tumors were observed. Della Porta et al. (*92*) administered HMT in the drinking water to CTM, SWR and C3Hf mice (1.25-12.5 g/kg body weight/day for up to 60 weeks) and to Wistar rats (1.5-2.5 g/kg body weight/day for 104 weeks). No treatment-related tumors were observed. Also negative was a subsequent study in which Wistar rats were given 2% HMT in the drinking water over three consecutive generations (*44*). No evidence for transplacental carcinogenicity was found. It seems clear that, in contrast to long term repeated subcutaneous administration in rats, chronic ingestion of HMT was not carcinogenic to rats and mice. A study by Klenitzky (*93*) in which "formol oil" was applied 50 times to the cervix uteri of mice (strain unknown) resulted in no tumors. It is difficult to interpret this experiment, however, because no information is available on the nature of the material used or on the quantities applied.

Discussion of Laboratory Findings

At present only one study unequivocally demonstrates the carcinogenicity of formaldehyde. This is the study by Swenberg et al. (*79*) which showed a nasal tumor incidence of 20% in rats killed after 18 months exposure to 15 ppm of formaldehyde vapors (the cumulative cancer incidence in the 24-month exposure study is presently not known). No exposure-related tumors have as yet been found in mice which were simultaneously exposed to the same concentrations of formaldehyde. In order to clarify the significance and validity of the CIIT study which, so far at least, appears to be unique in its clear demonstration of formaldehyde carcinogenicity, we will discuss a series of questions which it raises.

(1) Is there any other evidence supporting the results obtained by Swenberg et al. (*79*)? The answer is yes. In the study reported by Laskin et al. (*82*), rats exposed to formaldehyde, hydrogen chloride, and BCME developed nasal squamous cell carcinomas. There is reason to believe that formaldehyde was a major, if not the only, etiological factor (see above). There is evidence that both formalin and HMT (which releases formaldehyde *in vivo*) cause sarcomas in rats when injected repeatedly over long periods of time (*89*, *90*). It has been reported that exposure of the oral mucosa of rabbits to formalin causes advanced preneoplastic lesions (carcinoma *in situ*) (*87*). Formaldehyde has been reported to cause transformation *in vitro* in a mammalian cell line (*88*). Formaldehyde has been shown to be genotoxic in many different test systems (see section on formaldehyde mutagenesis). A closely related aldehyde, namely acetaldehyde, was recently reported to cause nasal cancers (5%) and laryngeal cancers (14%) in hamsters chronically exposed by inhalation to 1650-2500 ppm for 52 weeks (7 hr/day, 5 days/week) (*94*).

(2) Is the carcinogenicity of formaldehyde restricted to only one species, the rat, and only one tissue, the nasal mucosa? Several references cited above suggest that it is not. Species other than rats and tissues other than nasal epithelium seem to be susceptible to the carcinogenic activity of formaldehyde. However, considerable differences in degree of susceptibility may indeed exist. Lesions interpreted to be carcinomas *in situ* were induced in the oral mucosa of rabbits (*87*). Sarcomas were produced by repeated SC injections of formaldehyde

and HMT into rats for many months (*89, 90*). Neoplastic transformation of mouse Balb/3T3 cells in culture has been demonstrated (*88*). Chronic inhalation of the closely related short chain aliphatic aldehyde, acetaldehyde, has been reported to cause not only nasal but also laryngeal carcinomas in hamsters (*94*).

The nature of the differences in species susceptibility is not clear (such differences exist, however, with almost all carcinogens); they could arise at various levels of organization (physiological, defense mechanism, pharmacokinetics, metabolism, repair capacities). An interesting parallel is the relative resistance of hamsters to BCME as compared to rats (*83*).

(3) Why is the nasal mucosa seemingly the only target tissue in rats for the carcinogenicity of inhaled formaldehyde? Nasal mucosa is directly exposed to formaldehyde and may receive the highest dose although differences in tissue sensitivity and metabolism might also be involved. It should be mentioned that formaldehyde is not the only chemical carcinogen affecting the nasal mucosa. Other carcinogens, in addition to BCME, (including systemic ones) also cause nasal tumors of susceptible hosts, for example, various nitrosamines as well as dioxane and ethylene dibromide (*95*). The experimental induction of nasal tumors in laboratory animals is thus not a rarity and does not necessarily involve direct contact, through inhalation, with the nasal mucosa of the test compound.

(4) Is the viral infection which was noted in the CIIT study likely to be a significant factor in the nasal tumor development of the formaldehyde exposed animals? The possibility that the infection (presumably caused by a corona virus) contributed to the carcinoma response in this study cannot be discounted, but the panel considered it unlikely, because the signs of infection occurred during a very short portion of the experiment (at most a week) and the first detected nasal tumors had probably already formed at the time of the infection. Although the outbreak of sialodacryoadenitis introduced an uncontrolled variable into the experiment, it is unlikely that the transient viral infection affected the outcome of the experiment. It is important to consider that people exposed to formaldehyde may also experience viral infections of the upper respiratory tract.

(5) Are the irritant effects of formaldehyde likely to contribute to its carcinogenicity? "Irritation" is a poorly defined term. As Berenblum pointed out long ago, this term is "a vague generalization representing many different kinds of injury or stimulation of the tissues" (*96*). A more specific effect that has been included under the generic term of "irritation" is the induction of epithelial hyperplasia. Many studies on this topic estimate the degree of irritation by the level of hyperplasia induced in target tissues. The role of irritation in carcinogenesis has been investigated since the early years of chemical carcinogenesis research (*96*).

More recent studies have provided evidence on the hyperplastic effects of several agents, and in some cases have provided qualitative and quantitative analyses of the tissue response. A number of agents were reported to induce epithelial hyperplasia in several types of tissues but they had no carcinogenic or tumor-promoting activity associated with them (*97-99*). The panel found no evidence that the induction of irritation or, more specifically, of epithelial hyperplasia is a sufficient condition for the carcinogenic activity of an agent.

There is, however, suggestive evidence that some agents that produce epithelial hyperplasia may play a role in the process of tumor promotion. It was found that previously initiated mouse skin exposed to a promoting agent for only a short time will develop a low level of tumor response. A high incidence of tumors may develop, however, when the short period of exposure to the promoting agent is in turn followed by exposure to an otherwise inactive irritant such as turpentine (*100*) or wounding (*101*). Repeated mechanical skin abrasion was recently found to have a promoting effect on mouse epidermis (*102*). It is therefore conceivable that the "irritant" effect of formaldehyde, or more specifically its induction of epithelial hyperplasia, may contribute to some extent to the expression of its carcinogenic activity through a mechanism enhancing the promoting or tumor growth stage of carcinogenesis. However, it must be added that our knowledge of this type of effect is still quite inadequate and not directly applicable to the reported carcinogenic effects of formaldehyde on the nasal mucosa.

(6) Are the cytotoxic effects of formaldehyde likely to be an important aspect of its carcinogenic activity? Most carcinogens have significant cytotoxic effects. Therefore, formaldehyde is not an unusual case. There are many reasons why cytotoxic agents which cause cell death and regenerative cell replication might enhance the carcinogenesis process: they increase the number of cells undergoing DNA synthesis [it is known that cells are particularly susceptible to malignant transformation prior to DNA synthesis at the onset of the DNA-synthesis phase of the cell cycle (*102*); they may force the carcinogen exposed target cells through the several cell divisions that seem to be required for "fixation" of the mutagenic or carcinogenic event (*104*); they may create selection pressures in tissues containing initiated cells favoring their proliferation and prop-

agation (*105*); and they may act as tumor promoters (*106*). In short, it is conceivable that the cytotoxic effects of formaldehyde may play a part in its overall carcinogenicity.

Conclusions

In assessing the current evidence for the carcinogenicity of formaldehyde in animals provided by the limited number of studies conducted to date, the panel comes to the following conclusions: (1) The CIIT study provides adequate evidence that inhalation of formaldehyde vapors causes nasal carcinomas in rats. (2) There is suggestive evidence that formaldehyde might be carcinogenic in other species and tissues other than nasal. (3) Formaldehyde should be presumed to pose a carcinogenic risk to humans.

Recommendations for Future Research

The following are recommendations for future research on the carcinogenicity of formaldehyde: (1) the pharmacokinetics of formaldehyde and its interaction with target tissue should be studied in several animal species; (2) studies of formaldehyde by other routes of administration (oral and dermal) should be initiated; (3) additional studies of neoplastic transformation of mammalian cells in culture are needed.

Epidemiology

Strengths and Weaknesses of Epidemiologic Methods

Epidemiologic methods for etiologic studies are designed to uncover disease and exposure relationships in human populations wherein the study groups cannot be experimentally manipulated. Individual studies must be evaluated in terms of the strengths and weaknesses of the study design, the summation of epidemiologic evidence from a variety of studies, however, requires different standards. Circumstances that allow an exposure associated with a disease to be judged a cause of the disease have been best described by Hill (*107*). First is the strength of the association. Second is the consistency of the observation. The evidence for causality is more persuasive when the association has been repeatedly observed under various circumstances by independent investigators using different methods. Third is the specificity of the association. When a specific exposure is associated with a certain disease, there is a strong argument for cause and effect. In light of multicausation of most diseases, however, the lack of specificity does not irrevocably discount a causal hypothesis. Fourth is the temporal relationship of the exposure and disease. Cross-sectional and case control studies are poorly equipped to settle this issue. Fifth is evidence of a dose-response gradient. Sixth is the plausibility and coherence of the hypothesis. The hypothesis should not conflict with generally accepted medical theory.

Completed, ongoing, and proposed epidemiologic studies discussed in this report must be individually evaluated according to the strengths and weaknesses of their design. Conclusions regarding an etiologic role for formaldehyde in disease processes must be drawn while considering findings against Hill's (*107*) points.

Review of Completed Studies

Information on acute and chronic health effects of formaldehyde in humans comes largely from the following two sources: case reports of individuals who were exposed to formaldehyde and cross-sectional studies in which measurements of cause (formaldehyde exposure) and effect (prevalence of symptoms, signs, and disease) were made at the same point in time. In addition, limited information is available from cohort and case-control studies in which the ascertainment of cause and effect relate to two different points in time.

In this report, the assignment of published studies into the above categories was made mainly to facilitate discussion on problems and strengths associated with each category. For the purpose of this report, acute effects were defined as those that develop rapidly after a single exposure, while chronic effects were considered those that do not become manifest immediately after exposure and that persist over a period of time. The acute health effects of formaldehyde have been well documented elsewhere (*108-110*). Therefore, individual studies reporting acute health effects of formaldehyde were not reviewed in detail.

Case Reports

Numerous case reports of health effects, presumably due to formaldehyde, are available. Contact urticaria was described in a 28-year-old woman who worked as a carver and model setter in a factory that made leather dresses containing small amounts of formaldehyde (*111*). She had urticaria almost daily, (severely on the hands, with occasional edema of the lips) during work days. During weekends and vacations, when she had no contact

with the leather, there was no evidence of the skin erruption. Similarly, Harris (*112*) described four persons who developed acute papulovesicular eczema following contact with urea-formaldehyde resins. The condition persisted until the workers were reassigned to areas without formaldehyde.

Sakula (*113*) reported a case of acute respiratory distress in a hospital laboratory technician following exposure to formalin. Severe bronchial asthma followed the slightest inhalation of formalin vapor, but the worker was free from attacks on weekends and holidays. A case of pneumonitis following heavy exposure to formaldehyde by inhalation has been reported (*114*). The case involved a 27-year-old neurology resident who spent 15 hr exposed to a high concentration of formaldehyde vapor during preparation of brain specimens for student demonstrations. The following week, after only 2 hr spent at the same activity, he developed acute respiratory distress including progressive dyspnea and chest tightness over a period of 15 hr. Chest x-ray showed increased interstitial markings with early edema. A decreased pulmonary function as measured by FVC, $FEV_{1.0}$ and MMEF was also noted on day 2 and day 24 after the onset of symptoms.* This is said to be the first report describing a clinical picture of acute pneumonitis in man following formalin inhalation.

Cross-Sectional Studies

Acute Effects. Most of the information on the acute health effects of formaldehyde comes from cross-sectional studies of workers, volunteers, and residents exposed to formaldehyde. Symptoms associated with formaldehyde exposure include eye, nose, and throat irritation leading to lacrimation, sneezing, shortness of breath, sleeplessness, tight chest, nausea, and excess phlegm (*115-121*). An outbreak of hemolytic anemia among patients on hemodialysis was described in a recent report (*122*). The outbreak occurred shortly after a new system using filters impregnated with formaldehyde resins was installed. When the filters were removed, hematocrit values returned to previous levels. The severity and incidence of some responses were related to the concentration of exposure. In addition, the extent of reported discomfort appeared dependent on the relative humidity and temperature of the ambient air (*115, 117, 123*).

At 0.1-3 ppm, most people experience an irritation of the eyes, nose, and throat (*115, 117, 123*). Effects of exposures at higher levels are not clear; with increasing concentration, however, the discomfort increases rapidly and many people can tolerate exposures of 4 to 5 ppm for only 10-30 min (*124*). Between 10 and 20 ppm, symptoms are severe, and it becomes difficult to take a normal breath. Exposures at 50-100 ppm and above may cause serious injury to the respiratory tract, such as pulmonary edema and pneumonitis (*124*).

Chronic Health Effects. Chronic health effects attributed to formaldehyde from cross-sectional studies include respiratory problems, dermatitis, neurologic difficulties, and menstrual and reproductive disorders. Schoenberg and Mitchell (*120*) studied five groups of employees from a filter-manufacturing plant to determine adverse effects of exposure to phenolic (phenol-formaldehyde) resin fumes. Groups currently exposed to phenolic resins showed an excess of chronic cough and/or phlegm when compared to previously exposed or "never-on-line" groups. In addition, after adjustments were made for differences in total cigarette consumption, workers on the present production line more than five years had a significantly lower $FEV_{1.0}$/FVC and MEF 50%/FVC ratio ($p \leq 0.05$) than the "never-on-line" group. These results suggest that long term exposure to phenol-formaldehyde resin fumes may lead to chronic airway obstruction. No systematic measurement of formaldehyde concentration was made during this study but, based on measurements by others, levels were estimated to be in the range of 0.4 to 0.8 ppm. Exceptionally high levels (8.8 to 13.5 ppm) occasionally occurred when cross-current fans were turned off during part of the sampling period. In this study every control subject was occasionally exposed to resin fumes, which may explain the high prevalence of acute symptoms such as eye irritation (80%), nose irritation (53%), and lower respiratory tract symptoms (47%) among "never-on-line" workers. Shift studies suggested a small reduction in lung function in the production line workers, whereas control workers showed a small increase. As noted by the authors, the limitations of this study include small numbers of exposed subjects, probable formaldehyde exposure among some controls, and the potential for selective bias commonly associated with cross-sectional studies. In addition, the possible role of the parent resins, phenol, and other exposure from the industrial process, such as acrylic fiber break-down products, prevents a clear determination that long-term exposure to formaldehyde may lead to chronic airway obstruction.

In a study of rubber workers exposed to hexamethylenetetramine-resorcinol (HR) resins, Gamble et al. (*125*) found more self-reported symptoms

*FVC = forced vital capacity, $FEV_{1.0}$ = one-second forced expiratory volume, MMEF = maximal mid-expiratory flow rate, same as mean forced expiratory flow during the middle half of the FVC (FEF 25-75%).

(itch, rash, cough, chest tightness, burning eyes, running nose, and persistent cough and phlegm) among HR-exposed than among nonexposed workers. Contrary to the previous findings (*120*), there were no differences in lung function at baseline among exposure groups. There were, however, significant differences in lung function measurements before and after the regular work shift for HR exposed workers, but not among the non-exposed. The resin investigated in this study used resorcinol as the phenol donor and hexamethylenetetramine (HMTA) as both a formaldehyde donor and a catalyst. There was no association between lung function and ambient levels of resorcinol, formaldehyde, hydrogen cyanide or ammonia. Mean concentrations of formaldehyde were 0.05, 0.02 and 0.04 ppm for HR-exposed, HR-not exposed, and control group, respectively. Decrease in pulmonary function was related to the quantity of respirable particulates obtained from personal samples. Chemical analysis of particulates, however, was not performed. It is unlikely that formaldehyde by itself was responsible for the change in pulmonary function for two reasons: (1) the exposure level of formaldehyde was very low and (2) no association between its level and decrease in pulmonary function was observed.

Eight cases of occupational asthma (three smokers and five nonsmokers) were reported among 28 members of the nursing staff at a hemodialysis unit where formalin was used to sterilize the artificial kidney machine (*125*). Recurrent episodes of productive cough accompanied by wheeze were a prominent feature and, for five persons, attacks had extended over the previous three years. Inhalation provocation tests were performed on five subjects with histories of recurrent attacks of wheezing. In two of these subjects the test resulted in asthmatic attacks like those experienced at work. Peak expiratory flow rates fell approximately 50% and wheezing began 2 and 3 hr after exposure to formalin and lasted for 10 hr to 10 days. Three of the five subjects had no respiratory reaction to inhalation of formaldehyde similar to that experienced in the dialysis unit. Two of the five had no symptoms, while one developed conjunctivitis. This latter patient developed redness, weeping and sensations of grittiness of the eyes when heavily exposed to formalin. In the absence of symptoms and exposure there was no apparent reduction in lung function. The authors suggest that although formalin may not have been the etiologic agent in all cases, it may have increased the susceptibility to other agents, which could, perhaps, explain the high incidence of bronchitis-like symptoms. In the absence of a comparison group, an alternative explanation of the asthma being attributable to chance alone still exists. However, the explanation is unlikely because of the high proportion of the staff which developed the symptoms and because of the positive responses observed after the inhalation provocation test.

Formaldehyde-related asthma and dermatitis were also reported by Kerfoot and Mooney (*121*). A survey of six Detroit area funeral homes showed that embalmers were generally exposed to formaldehyde at mean levels ranging from 0.25 to 1.39 ppm with a total range of 0.09-5.26 ppm. They experienced acute toxic effects including eye and nose burning, sneezing, coughing, and headaches. Asthma or sinus problems were reported by 3 out of 7 morticians. In addition, two workers experienced dermatitis, with one case being so severe that he discontinued working for a period of time until he recovered. Although it was the professed intention of the authors to correlate the formaldehyde concentrations in each funeral home with the irritant effects on embalmers who worked at the particular funeral home, no data were presented to that end in this study. A dosage effect was implied in the sentence, "The morticians who spent more time embalming than in general funeral work, also experienced more complaints of irritations." It was not clear who and how many people were in the study. Embalming agents contain formaldehyde as well as a variety of other chemicals, such as tissue moisturizers, smooth muscle relaxants, bleaches, an auxiliary antiseptic agent (phenol), dyes, buffers, wetting agents, water conditioners and/or anticoagulants, perfumes and odor suppressors, and vehicles (methanol, ethanol, and glycerine). In light of the possible mixed exposure to a variety of the above chemicals during embalming and the lack of an appropriate control group in the study, the relationship of formaldehyde exposure among embalmers to development of asthma and dermatitis remains inconclusive.

Yefremov (*127*) studied 278 workers at two wood-processing plants where urea-formaldehyde resins were used extensively. They reported that the incidence of chronic diseases affecting the upper respiratory tract was higher in workers exposed to formaldehyde than in a control group consisting of 200 individuals of corresponding ages. The prevalence was from 28.1 to 58.3% depending on work areas, among formaldehyde-exposed workers, compared to 13% among the controls. The highest prevalence of disease (58%) was observed in the workers at the hot press shop, where the concentration of formaldehyde was 2.5 times that in the cold press shop. Disease occurrence was 33.9% at the cold press shop. In all work areas the formaldehyde concentrations were reportedly below the max-

imum permissible concentration (0.4 ppm). Assuming the age-matched controls represent an appropriate comparison group (no mention was made of matching on sex and smoking history), this report supports the hypothesis that exposure to formaldehyde may lead to chronic respiratory diseases.

Kratochvil (*128*) examined a total of 18 workers of a mean age of 35 with an average formaldehyde exposure of 7 years in a clothing production plant. Formaldehyde exposure occurred during storage and processing of fabric impregnated with urea-formaldehyde and melamine-formaldehyde resins. Catarrhal conjunctivitis was found in 72% of the workers; 28% of the workers exhibited a catarrhal inflammation of the upper respiratory tract, 22% of the workers exhibited chronic bronchitis diagnosed in accordance with the criteria of the World Health Organization, and 11% of the workers showed skin changes. Lung function tests showed that the vital capacity and the differential forced vital capacity exhibited normal values for all workers. The concentrations of formaldehyde in these work areas were below the maximum allowable concentration (0.4 ppm). In the absence of an appropriate control group, an etiologic role of formaldehyde in development of the above conditions is uncertain. In fact, the 22% incidence of chronic bronchitis among the workers corresponded to the incidence of this condition reported for a normal population of a similar age group.

Shumilina (*129*) reported a high incidence of menstrual and reproductive function disorders among 446 women workers (130 finishers and 316 inspectors) exposed to urea-formaldehyde resins. Formaldehyde concentrations of 1.2 to 3.6 ppm were often found in the finishers' work area of the fabric trim shop, while levels from 0.04 to 0.56 ppm occurred in the inspectors' work area. A group of 200 saleswomen not exposed to formaldehyde was used for comparison. The reproductive disorders reported to be more common among those exposed included menstrual disorders, increased complication during pregnancy, and higher percentage of neonates with low birth weights. The role of formaldehyde in the development of these disorders is uncertain, however, because of the lack of information on the work environment and the socioeconomic status of the study and control groups. In addition, many of these disorders are known to be associated with physical and mental stress, personal habits (alcohol, cigarettes, caffeine consumption), nutritional status, and other factors related to the socioeconomic status of women. Still, these findings are intriguing and indicate a need for further studies in this area.

Neshkov and Nosko (*130*) reported a high incidence of sexual dysfunction among male workers employed in a plant producing glass fiber reinforced plastic. These workers were exposed to vapors of phenol, formaldehyde, aniline, epichlorohydrin, diphenylpropyl, styrene and a combination of glass fiber and glass-reinforced plastic dust. The levels of each of these chemicals were 1.5 times the respective maximum permissible level in 63% of the samples (maximum permissible level of formaldehyde is believed to be 0.5 mg/m^3 or 0.4 ppm). Among the 143 workers examined, 58 (40.5%) had psychoneurologic and sexual complaints. Sexual complaints included a diminution of libido, premature ejaculation, a weakening erection and decrease in the satisfaction derived from an orgasm. Analysis of the sexual complaints revealed a direct relationship to the duration of employment at the plant. Testicular dysfunction among the workers was also reported, including decreased volume and increased viscosity of ejaculate and decreased number of spermatozoids. The authors concluded that these sexual dysfunctions were the results of complex toxic effects of chemicals on the cells of the cortex and those of the subcortical brain stem structures, which participate in the regulation of sexual function. It is impossible to determine how much of the sexual dysfunction might be attributable to formaldehyde since appropriate control groups were not included and these workers were exposed to a variety of toxic chemicals in addition to formaldehyde. Of particular interest are reports of epichlorohydrin-induced sterility in animals (*131*, *132*).

Ishchenko and Pushkina (*133*) compared morbidity and sick leave among 662 workers engaged in the manufacture of phenol-formaldehyde resins to that among 473 unexposed workers. Several disease conditions were more common in the formaldehyde exposed group than in the controls, particularly from diseases of the respiratory tract (1.8-fold among males and 1.4-fold among females). Among women, the frequency of urogenital problems was 2.3 times more common in the exposure group. Days absent from work due to illness among those exposed exceeded controls 1.5- to 1.6-fold. Although the authors state that the age distribution of the exposed and comparison populations was similar, no description of the methods used to determine morbidity (examination, self-report, or medical records) was provided. In addition, uncontrolled social factors, as recognized by the authors, may play a role. In light of these limitations, the greater number of lost workdays due to sickness and the increased evidence of respiratory and urogenital diseases among the exposed workers, although suggestive, does not provide definitive evidence concerning the role of formaldehyde.

In a mail survey of 20 funeral homes in Los Angeles (*134*), 57 of 80 embalmers responded. Nine (16%) reported symptoms compatible with acute bronchitis and 17 (30%) were considered to have chronic bronchitis. The 31 asymptomatics, however, had worked longer than the bronchitics (18 years vs. 11 years). In the absence of a control group, these findings are, at best, suggestive.

Engel and Calnan (*135*) reported an outbreak of dermatitis in a car factory. A total of 50 cases of dermatitis were observed in three years (1962-1965) among 150 employees who handled rubber weather strips coated with phenol-formaldehyde resins. The workers who developed dermatitis had been exposed to the adhesives containing phenol-formaldehyde resins for from one day to two years before the onset of the eruption, with an average period of contact of 17 weeks. The average duration of the eruption was 12 weeks, however, in three cases it persisted up to 2½ years. The eruption was generally an erythematous vesicular rash of the fingers and hands. Three materials were handled by these employees: (1) the rubber weatherstrips, used for some years; (2) adhesive A and B introduced 4 years before in 1962 and supplied by the same manufacturers; (3) toluene, which was the solvent used to activate the adhesive. The rubber weatherstrips alone were ruled out as a cause because they came from various suppliers and had not changed in composition for a long time. The toluene would not be expected to cause sensitization within a short period of time. Among the 29 patch-tested dermatitis patients, four (14%) gave a weak reaction to phenol alone, while 65% had a positive reaction to the adhesive resins. It is, therefore, probable that formaldehyde in the resins was a causal agent. Outbreaks of dermatitis in several industries using formaldehyde resins were reported by Schwartz, Peck and Dunn (*136*). In a factory where plywood was laminated, 600 cases of dermatitis were reported among about 800 workers during the first six months of operation. In a second reported outbreak, over 40 workers out of a total of 100, developed dermatitis in a factory making tool handles from laminated glass fabric and phenol-formaldehyde resins. Although no unexposed group was available for comparison, the high proportion of formaldehyde exposed workers developing dermatitis is quite impressive.

In a hemodialysis unit where formalin was used as a sterilant, 6 to 13 staff members developed dermatitis within 3 weeks (*137*). Four of the six were positive in patch tests with 3% formalin. It was not clear why only the hemodialysis unit was affected, since other units also used formalin. The author speculated it might be due to the use of a detergent that lowered the resistance of the skin to formaldehyde vapors and to the high temperature and concentration of formalin in the preparation room. Lack of controls hampers the interpretation of these data.

Cohort and Case-Control Studies

The panel was not aware of any published cohort of case-control studies designed to evaluate the role of formaldehyde in the development of disease or abnormal conditions. Many mortality studies have been reported of workers from occupations or industries wherein formaldehyde exposure may have occurred. For example, Moss and Lee (*138*) have reported elevated risks of oral and pharyngeal cancer among male textile workers. They reported 77% excess deaths due to these cancers compared with the male population of Wales and England. These textile workers may have been exposed to formaldehyde, since formaldehyde has been widely used in the textile industry for producing creaseproof, crushproof, and shrinkproof fabrics. No environmental measurements of formaldehyde, however, were made in this study. A recent NIOSH survey showed concentrations of formaldehyde in the textile plants in the U.S. ranging from 0.1 to 1.4 ppm.

Bross et al. (*139*) reported a significantly increased risk of nasal cancer among brickmasons, textile workers and shoemakers. Textile workers also had significantly elevated risk of cancer of the pancreas and stomach. No information on formaldehyde concentrations was reported.

Decoufle (*140*) has reported significantly increased risks of cancer of the buccal cavity, pharynx and larynx among male leather workers. Bladder cancer and malignant lymphomas were also associated with increased risks among male and female employees in the leather industry. The cancer risk for the employees was calculated relative to the risk for those who were in clerical positions. A variety of chemicals including formaldehyde, azo dyes, chromium compounds and tanning extracts have been used in the production of leather goods. Some of these chemicals are carcinogenic in animals. Industrial hygiene surveys of a calf skin tannery in the U.S. showed concentrations of formaldehyde in the finishing department ranging from 1 to 8.6 ppm (*141*).

Matanoski (*142*) reported an excess of primary liver cancer and lung cancer among pathologists compared to radiologists. However, oral and pharyngeal cancers were lower in the pathology group. Although exposure estimates were not available,

pathologists are more likely than radiologists to be exposed to formaldehyde.

Although the above investigations were not designed to study health effects of formaldehyde, the results suggest the possibility of formaldehyde being carcinogenic in humans. The lack of precise information concerning the number of persons exposed to formaldehyde and the level of exposure, in addition to the problems of confounding exposures, makes interpretation of these reports regarding formaldehyde difficult.

Conclusions

In summary, a wide variety of acute and chronic health effects from formaldehyde exposure have been reported. They include eye, nose and throat irritation, headache; shortness of breath; wheezing; dermatitis; chronic cough; excess phlegm; chronic airway obstruction; asthma; bronchitis; rhinitis; pharyngitis; menstrual and reproductive disorders; sexual dysfunction; and possibly cancer. These studies were primarily of a cross-sectional design, thus, they do not allow a clear determination of the order of events. In addition, many studies lacked appropriate controls and/or environmental measurement, making it difficult to clearly evaluate the role of formaldehyde. Independent reports of respiratory system disorders and dermatitis among persons from a variety of work settings supply evidence on the consistency of the association, and indicate that formaldehyde is a likely contributor to the origin of these diseases. Only three studies (*120*, *125*, *127*) allowed an estimate of the strength of association between formaldehyde and respiratory disease. The risk of chronic respiratory symptoms among exposed groups ranged from about 1.5 to 4.5 times that among nonexposed groups, with little evidence of a dose gradient. The studies of dermatitis among workers exposed to formaldehyde, although reporting a high prevalence, lacked comparison populations necessary to estimate the strength of the association. Respiratory and integumentary systems are plausible response sites since workplace exposure to formaldehyde is likely to occur by inhalation or dermal contact.

The report of excessive menstrual and reproductive problems among women exposed to formaldehyde is provocative and, despite the study limitations, indicates the need for further research in this area. No reports of studies specifically designed to evaluate the carcinogenicity of formaldehyde in human populations were available, but several such studies are in progress.

Review of Planned and On-Going Epidemiological Studies of Formaldehyde

Planned and on-going investigations related to formaldehyde exposure include one study of a new technique of measuring formaldehyde, three studies investigating complaints, four epidemiological studies of morbidity (cross-sectional and prospective), and six mortality studies (cohort, proportionate mortality, and case-control). The questions being addressed and an evaluation of each group of studies follows.

Measurement Technique

The use of solid absorbent surfaces for collecting personal samples of vapor and particulate formaldehyde is being examined. This method should be more sensitive and efficient than the present impinger method, thereby permitting more accurate assessment of environmental exposures. An occupational study (cross-sectional morbidity) is planned, but details have not yet been provided.

Investigation of Complaints Relating to Formaldehyde

The results from three states are being compiled. In Connecticut, persons complaining of health problems due to urea-formaldehyde insulation completed a questionnaire concerning their symptoms and air levels of formaldehyde were measured in their homes. Occupants 489/794 of 262 residences presented complaints, the most common symptoms being eye, nose, and throat irritation, and headaches. Formaldehyde concentrations ranged from 0 to 10 ppm (mean of 1.5 ppm). About half of the complaints were associated with levels of 0.5 to 10 ppm.

F. Marshall of the New Jersey Department of Health obtained medical histories, all available information on insulation, and patterns of health effects from residents with recently installed urea-formaldehyde foam insulation who complained of formaldehyde odor, irritation, or increased pre-existing illness patterns. In 40/55 homes investigated, the most common symptoms were tearing of the eyes, sore throat, cough, and runny nose. Air samples were collected in 22 homes. In 14 homes where formaldehyde was detected, levels ranged from 0.01 to 0.78 ppm.

In New Hampshire, the Bureau of Occupational Health (M. Hilgemeier) administered a standard questionnaire to residents with complaints associated with formaldehyde exposure. Standard NIOSH

techniques were used to collect formaldehyde samples. About 90% of the samples were below 0.5 ppm; 10/77 dwellings were mobile homes.

The above studies on formaldehyde complaints are all similar and suffer the same deficiencies. None of them can be used to estimate prevalence of symptoms nor can they be used to establish dose-response relations. These shortcomings include: (1) the surveys are conducted only among those who complain, and although the prevalence of symptoms should be high, it is a biased sample; (2) there are no controls and no measurement of other irritants that could cause health complaints. Thus, these studies are only suggestive of possible problems and by themselves provide little evidence of cause and effect relationships.

Morbidity

R. Levine of the Chemical Industry Institute of Toxicology studied approximately 100 West Virginia morticians in a cross-sectional study of lung function (spirometry) and respiratory symptoms. Employment and smoking histories were also obtained. Industrial hygiene measurements made in the mortality study of Ontario embalmers along with symptoms during embalming, number of bodies embalmed, subjective assessment of severity of fumes, and length of employment will be used to assist in the estimation of exposure in this study. Spirometry will be compared to predicted values from Knudson, and internal comparisons will be related to exposure after age, height, and smoking adjustments. Data from this study are being analyzed in terms of the prevalence of respiratory symptoms (cough, phlegm, dyspnea) and the relation of percentage of predicted pulmonary function to employment (formaldehyde exposure) after adjustment for confounding variables. There is no assessment of skin effects. It is not clear if acute symptoms related to exposure are to be evaluated. Although there is a good rationale for studying this occupational group, an inability to detect a significant response in this study could be due to low cumulative exposure (probably less than 8 hr/day). Length of exposure (years worked or latency) should be adequate. If we assume 50 persons each (smoking groups combined) in a high and low exposure group (the optimal situation) there is an 85% chance of correctly rejecting the null hypothesis of no difference in FEV between exposure groups, if the true difference is 0.5 liters and α level is 5%. If the symptom rate is 20% in the low exposure group, there is less than a 50% chance of correctly rejecting the hypothesis of no difference if the true difference is 20% at the 5% level (two-tailed test). As in all cross-sectional studies, estimates of exposure are only a crude indicator of actual exposure. This is, however, one of the few studies to attempt to assess long term effects of formaldehyde on lung function. Although embalming fluid contains 1-2% formaldehyde, other pulmonary irritants are also present (e.g., phenol) but these may be at low enough concentrations to have a minimal effect. A comparison group (e.g., funeral directors) would have provided more confidence in the results and more power in the analysis.

The remaining three morbidity studies are of residents in homes with urea-formaldehyde (UF) foam insulation. In the first of these, M. Thun of the New Jersey Department of Health identified about 400 homes that had been insulated with UF foam and an equal number of control homes. Information gathered by telephone interview included type of home and insulation, formaldehyde odor, health symptoms and other medical data, demographic data on the occupants, and the period prevalence of asthmatic attacks, wheezing, chest pain, stinging or burning skin, burning or tearing eyes. Except for wheezing, the controls reported a higher prevalence of symptoms than did UF foam households. There was no detectable difference in the overall incidence of new symptoms during the year. There was, however, an association of increased symptoms and formaldehyde odor; the incidence of new symptoms following installation of the insulation was 2.7 times higher than in the months preceding the insulation. About 64% of the residents of the UF foam homes reported no problems at all related to the foam insulation. There is the possibility of selective recall in the remaining 36% of the study group because of the possible publicity relating to mobile homes and the specific questions relating to insulation. Despite this potential bias, there was little overall difference between study and comparison populations. There was, however, a dose-response relation (dose was based on odor). Unfortunately, there were no environmental measurements to correlate with odor perception and symptoms, and apparently no control of other potentially confounding irritants other than formaldehyde. The added insulation may have also increased other respiratory irritants that could have raised the symptom rate. It is not clear how the formaldehyde odor was described to the subjects. This study has been completed recently and should be available for review shortly. The summary given the Panel suggests little difference between the insulated and control homes except when odor occurred.

M. Woodbury and C. Zenz of the Wisconsin Department of Health and Social Studies are proposing to study 110 new mobile home owners. Expo-

sure measurements are to be made twice monthly for 9 months. It is difficult to evaluate this prospective study because of the lack of detail provided. Some of the questions that need answering are: What are the health parameters that will be determined and how often are they being monitored? Are there formaldehyde controls for the mobile homes? If so, how are they selected? If no controls are planned, the study will have limited value. Are other respiratory irritants being measured (e.g., NO_2)? About 50% of the homes are newer homes with higher formaldehyde levels than the older homes which are serving as controls and have measurable but low levels of formaldehyde. Assuming a 20% symptom rate and 180 people in each exposure group (high and low formaldehyde), there is about an 85% chance of correctly rejecting the hypothesis of no differences in symptoms when the true difference is 15% at the 5% α level, and about a 99% chance of correctly rejecting the hypothesis of no difference in FEV_1 when the true difference is 500 mL at the 50% α level (two-tailed test). The effects of long-term chronic exposure cannot be estimated by this study. These investigators also performed a retrospective pilot study of 65 mobile home residents. The data will be mainly useful in the planning and execution of the prospective study.

L. Williams of the Oregon Department of Disease Monitoring and Control is planning to study 300 mobile home residents who responded to a health questionnaire. The volunteers were from two regions, coastal and inland. The purpose of the study is to ascertain the effect of humidity, temperature, and wind ventilation on "health effects to potential formaldehyde exposure." Inasmuch as the participants in the study are volunteers, however, it is not a random sample. Apparently, environmental measures are planned, but it is not known what other information on insulation, demography, other pulmonary irritants, humidity, temperature, etc., will be collected. Although the details are unknown, this study design does not promise to add very much to our knowledge. The power in this study is similar to the study by Woodbury and Zenz when the following assumptions are made: (l) the two exposure groups to low and high formaldehyde are of equal size ($\sim$ 150); (2) the prevalence of symptoms is about 30% in low exposure group.

Mortality

H. Weiss of the Wisconsin Department of Health and Social Sciences conducted a case-control study of infant mortality by type of residence and found an increased risk for mobile home residents. Socioeconomic status is only one of many sources of potential bias in this study. The completed study should be reviewed, but the short description available suggests that the data will provide little, if any, useful information on the effect of formaldehyde.

D. Grauman of the National Cancer Institute proposes to evaluate the mortality experience (using standardized mortality ratios [SMR] of a cohort of about 11,000 medical technologists. This group is exposed to other chemicals in addition to formaldehyde (e.g., chloroform and benzidine). No environmental data are available, so there cannot be a good estimate of exposure-response relationships. A positive association will not be conclusive because of the mixed exposure. A negative association will not be conclusive because of the lack of exposure information and the possibility of low exposures. The control group is to be the U.S. population. If 15% of the cohort are dead (n = 1650 cases) and if 20% of the deaths in the control population were from cancer, there would be better than a 95% chance of correctly rejecting the hypothesis of no difference between exposed and controls if the true differences were 5% at the 5% α level. Assuming 1/4 of all cancers were lung cancer, there is about an 80% chance of correctly rejecting the hypothesis of no difference if the true differences were 5% at the 10% α level (two-tailed test).

There are three mortality studies of embalmers. J. Walrath is conducting a proportionate mortality ratio (PMR) analysis of about 1500 morticians from New York. The purpose is to determine whether there is an excess proportion of deaths due to specific malignant neoplasms compared to the general population. Besides having the problems inherent in a PMR analysis where the population-at-risk is not available there is little exposure data (length of exposure is estimated on the basis of the year first licensed). Assuming the rate of lung cancer is 5%, there is better than a 99% chance of correctly rejecting the hypothesis of no difference in lung cancer rates when the true difference is 5% at the 1% α level (two-tailed test). Walrath is also conducting another PMR study on about 1200 embalmers from California. This study is very similar to the one in New York, except there will be more information on length of exposure which can be evaluated. There is, however, no direct estimate of exposure or smoking history or other confounding exposures. If 20% of the deaths were from cancer, there would be a better than 90% chance of correctly rejecting the hypothesis of no difference in cancer rates between exposed and controls if the true differences were 5% at the 10% α level (two-tailed test). R. Levine of the Chemical Industry Institute of Toxicology is also studying embalmers

using an SMR retrospective mortality design. The cohort is composed of Ontario's funeral service professionals licensed during 1914-1967. Date of birth, date of first licensure, type of license, years licensed, and place of employment are available for each person. Observed mortality rates will be compared to Canadian national and provincial mortality data. Mortality will also be analyzed as a function of exposure (years worked?). A retrospective industrial hygiene assessment will consist of inquiring about changes in funeral practices with time, surveying several selected funeral establishments. The survey will include air sampling for agents of potential health concern (e.g., formaldehyde, phenol) and examination of purchase records to determine amount and kind of chemicals used. Presumably these data are to be used in evaluating dose-response relationships. Assuming the study population comprises 180 deaths (15% of the estimated cohort) and a 20% cancer rate there is about a 50% chance of correctly rejecting the hypothesis of no difference if the true difference is 10% at 5% α level (or an 85% chance if the true difference is 15% at the 5% α level). As a group, these three studies of embalmers should provide a good estimate of potential risk from formaldehyde exposure.

A. Blair at NCI and the Formaldehyde Institute are collaborating on a proposed cohort mortality study to develop age, race, and sex-specific mortality rates among formaldehyde-exposed workers. Rates will be compared with those in the U.S. population and local or regional populations where appropriate.

The first phase of the investigation is to determine if there is a suitable cohort for study. Suitability will be based on representatives of the participating companies, range of exposure, availability of a cohort of at least 3,000 workers with a minimum 15-year latent period, suitable age distribution, and sufficient information for adequate follow-up. If the requirements for a scientifically sound study are met, the study will proceed. Formaldehyde exposure for each individual will be estimated using job titles, work locations, past environmental measurements, years of employment, and the presence of potentially confounding exposures. The exposed group will be stratified by intensity and duration of exposure, age and year of first exposure, susceptibility, and latency.

The cohort should be large enough to engender confidence in the differences in mortality experience of study and comparison populations. Although exposures are unlikely to be pure formaldehyde, because of the varied occupational exposures and size of the cohort, it may be possible to assess the individual contribution of formaldehyde. Although the assessment of exposure is retrospective, it can still be at least semiquantitative. This is a very important part of this study and should employ a full-time industrial hygienist following methods similar to those of Emsden at the University of Pittsburgh. It is important that all companies participate in the study, as the results may be seriously biased if some do not.

Conclusions

Of all the mortality studies proposed, those examining the medical technologists, embalmers, and formaldehyde workers are the only ones that can assess the carcinogenic risk among those individuals exposed. Although single epidemiologic studies usually cannot adequately assess an occupational risk, or the risk of exposure to a chemical agent, taken together these studies should help clarify the situation. There are, however, a number of concerns about these studies.

- Are exposures to formaldehyde high enough in these populations to assess possible effects? For example, are embalmers exposed 8 hours/day, 5 days/week, or is their exposure much less?
- Can exposure history be adequately documented? Are individuals with little or no embalming experience distinguishable from those with considerable exposure? Since few if any of the workers are exposed only to formaldehyde, what is the effect of exposure to these other agents?
- Is exposure to formaldehyde in the same range as for other populations?

The confidence we place in the findings from these studies depends largely on the ability to retrospectively estimate exposure. If exposure in these occupational groups is representative of other exposed populations, the conclusions may be indicative of potential risk to all exposed populations. If these studies do not adequately address the above questions, then further investigation may be required. Such investigation may be pursued within the existing data set, or new populations may need to be investigated.

Recommendations for Epidemiologic Research

There is a need for carefully designed epidemiologic studies to evaluate the role formaldehyde may play in the origin of certain chronic diseases. Specific research areas identified by the panel include the following: (1) additional studies of chronic respira-

tory system disorders that include environmental measurements to allow a more precise estimate of risk at various exposure levels, including industrial, as well as mobile home populations; (2) projects designed to confirm or deny the association of menstrual and reproductive disorders and formaldehyde exposure reported by Shumilina (*45*); (3) more complete epidemiologic studies to evaluate the carcinogenicity of formaldehyde in human populations. Although several projects are under way, there is a need to be alert for resources for additional research. The widespread use of formaldehyde in industry and its occurrence in a variety of consumer products may provide opportunities for other studies. The many uses of formaldehyde are summarized in the NIOSH Criteria Document (*108*) and will not be itemized here. It is sufficient to say that the chemical is of importance in adhesives for particle board and plywood production; resins to mold a variety of plastic parts for automobiles, appliances and hardware; wrinkle-resistance in textile manufacturing; strengthening of various paper products (grocery bags, wax paper, napkins and tissues, and filter paper); specimen preservation; mildew prevention; insulation; and protective coatings.

It may be possible to identify other formaldehyde-exposed cohorts for study. The major difficulty is that, for most occupations or industries, only a small proportion of the workers have actual contact with formaldehyde. This is clearly demonstrated from the NIOSH Occupational Hazard Survey, Phase I, 1972-1974, where 4,636 plants were studied in over 600 different industry types (according to S.I.C. codes). These plants employed 895,725 workers in 453 different occupations. Products containing formaldehyde were encountered in 396 separate S.I.C.-coded industries. Table 1 lists the percentage of workers exposed to formaldehyde in the industries with the larger work forces, and those of particular interest.

This survey confirms an impression given by published reports that exposure to formaldehyde is more common in medical and laboratory environments and in certain parts of the textile, wood, and paper industries. In certain industries, however, the number of work places and workers studied was small and the survey may not have included those where significant exposure to formaldehyde occurs (e.g., the chemical manufacturing industry).

The Industry-wide Studies Branch of NIOSH is carrying out an industrial hygiene study of formaldehyde exposure in several industries in search of a suitable cohort for a mortality study of formaldehyde exposed workers. Measurements will be made in industries concerned with formaldehyde manufacture, textile and clothing production, wood furniture and wood and paper product manufacture. Fifteen site visits are planned and these will be completed over the next six months.

Table 1. Percentage of workers exposed to formaldehyde.

Industry	% of workers exposed
Medical	
Veterinarian and animal hospitals	23.0
Funeral services	100.0
Medical laboratories	31.0
Construction	
Forestry services	10.5
General building contractors	3.6
Heavy construction	3.7
Plastering and lathing	5.4
Textiles	
Finishing plants (synthetics)	11.6
Coated fabrics	14.0
Hats and caps	47.0
Fabricated textile products	3.3
Wood and paper	
Veneer and plywood	21.0
Wood products	8.6
Upholstered furniture	12.2
Paper mills	5.8
Paper coating and glazes	9.0
Bags (except textiles)	11.1
Paints and allied products	16.9
Fabricated rubber products	29.0
Abrasive products	11.0

The major difficulty of the mortality studies of individuals exposed to formaldehyde is the limited ability of such studies to detect excess risk for rare causes of death. Since the known carcinogenic action of formaldehyde is limited to the nasal sinuses in rats, there is a need to evaluate the risk for this site in man, although it is clear that carcinogens may not affect the same tissues in humans as in laboratory animals. It is unlikely that a cohort of sufficient size can be assembled to accomplish this task; however, a carefully designed case-control study might. The panel suggests that the feasibility of performing a case-control study of cancer of the nasal sinuses in areas where there is heavy production or use of formaldehyde as a vapor should be explored.

Evaluation of Risk

Nasal Tumor Risk in Rats Due to Formaldehyde Inhalation

Existing data on humans exposed to formaldehyde provide no quantitative estimates of the incidence of irreversible diseases. Epidemiologic studies are in progress which may be useful in identifying

and estimating chronic disease risk due to formaldehyde vapor exposures.

A study was sponsored by the Chemical Industry Institute of Toxicology to investigate the toxic effects of inhalation of formaldehyde vapor in Fisher 344 rats and B6C3F1 mice. Animals were exposed to average dosages of formaldehyde vapor of 0, 2.1, 5.6 and 14.1 ppm for 6 hr/day, 5 days/week, for 24 months. A total of 120 animals/species/sex were exposed at each dosage level. Within each group, 10 animals were sacrificed at 6 months, 10 animals at 12 months and 20 animals at 18 months. The frequency of nasal tumors in Fischer 344 rats through the 18 month sacrifice was reported by Swenberg et al. (*79*). Since no significant differences were noted in the frequency of nasal tumors between sexes during the first 18 months of exposure, the results for the sexes were combined. No nasal tumors were observed prior to 12 months. The results given are summarized in Tables 2 and 3.

Tumors in two categories were considered for risk analysis: squamous cell carcinoma and total nasal tumors. Since time-to-tumor data were not presented by the authors risk analyses are performed only on the unadjusted tumor rates of animals dying with tumors prior to 18 months. The number of unscheduled sacrifice animals at risk for the combined sexes prior to 18 months is 200 per dose.

Using a procedure given by Crump et al. (*143*), the multistage model of carcinogenesis was fit to the proportion of animals dying with tumors before 18 months. Note that this analysis does not give the probability of death due to tumors. Time-to-tumor and cause of death data are not given by Swenberg et al. (*79*); hence a competing risk analysis utilizing the sacrificed animals cannot be performed. The upper 95% confidence limits for the proportion of animals dying with squamous cell carcinomas before 18 months were 0.3, 2.0 and 17.1% for 2.1, 5.6 and 14.1 ppm, respectively. Even though no squamous cell carcinoma were observed at the two lower dosages, because of statistical uncertainty there is no guarantee that squamous cell carcinomas cannot occur at 5.6 ppm or less in Fischer 344 rats within 18 months.

Since the true form of the dose response curve below 2.1 ppm is unknown, nasal tumor rates in rats exposed below this level cannot be predicted directly. Since the dose response is curving upward (convex), the potential nasal tumor rates at lower dosages are predicted to be proportionately lower than the potential risk at 2.1 ppm. The upper confidence limit on the rate of squamous cell carcinomas is 0.3% at 2.1 ppm. At 1 ppm the risk is predicted to be at least a factor of 2.1 lower, i.e., 0.003/2.1 = 0.0014, etc. In general, proportional dose response predictions (linear extrapolation) for dosages below 2.1 ppm are given by: Squamous cell carcinoma rate $\leq 0.0014 \times$ dosage (ppm).

Similarly, the upper 95% confidence limit for the proportion of animals dying before 18 months with

Table 2. Frequency of nasal tumors in animals dying prior to 18 months.

Dosage, ppm	Number dying	Tumor frequency		
		Squamous papilloma	Squamous cell carcinoma	Spindle cell sarcoma
0	2	0	0	0
2.1	2	0	0	0
5.6	8	0	0	0
14.1	44	4	28	1

Table 3. Frequency of nasal tumors in animals sacrified at 18 months.

Dosage, ppm	Number examined	Tumor frequency	
		Adenomatous polyp	Squamous cell carcinoma
0	40	0	0
2.1	40	1	0
5.6	40	1	0
14.1	40	1	8

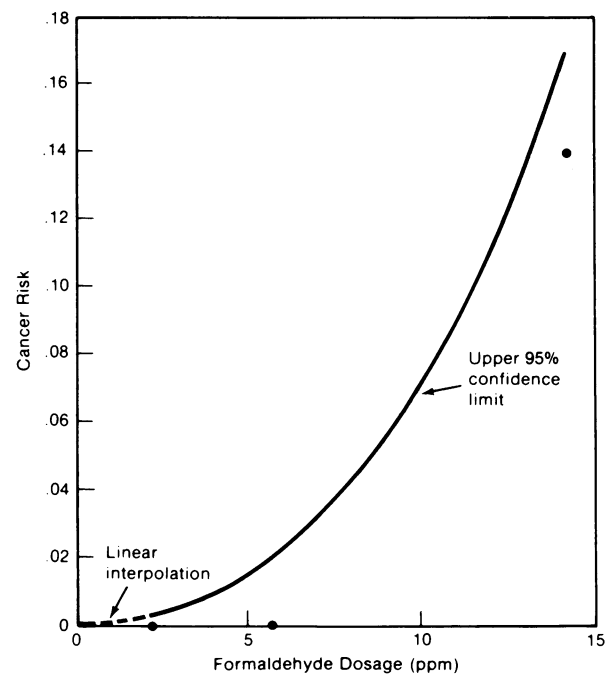

FIGURE 4. Potential proportion of Fischer 344 rats dying with squamous cell nasal carcinomas before 18 months.

any nasal tumor is 0.33%, giving: Total nasal tumor rate $\leq 0.0016 \times$ dosage (ppm). For example, the proportion of animals dying before 18 months with squamous cell carcinomas in Fischer 344 rats is predicted to be no more than 1.4 per 1000 animals at an exposure of 1 ppm formaldehyde for 6 hr/day, 5 days/week. The low dose extrapolation procedure is illustrated in Figure 4.

The rat data indicates a potentially high nasal tumor rate at inhalation exposure levels comparable to levels which can be experienced in homes and occupational environments. Perhaps the epidemiology studies in progress will provide direct tumor risk information for humans exposed to formaldehyde.

Conclusions

The metabolic pathways for formaldehyde in various animals species and man are qualitatively the same but differ in rate with formaldehyde or a formaldehyde adduct likely to be the carcinogenic agent.

Most of the studies available on the possible teratogenicity or reproductive effects of formaldehyde are inadequate for evaluation and none are adequate for exposure by inhalation.

Formaldehyde is mutagenic in a variety of test systems, including bacteria, yeasts, fungi, insects and mammalian cells and causes mutations and chromosome aberrations.

By inhalation formaldehyde is carcinogenic to the Fischer 344 rat, producing nasal tumors at dose levels that are within the same order of magnitude as those to which humans are exposed.

Formaldehyde may be carcinogenic to species other than the rat and to tissues other than nasal.

Formaldehyde should be presumed to pose a carcinogenic risk to humans.

No information is presently available whether (a) certain individuals may be at greater risk of cancer from formaldehyde exposure, (b) tumors may be expected to arise at nonrespiratory sites as a result of inhalation of formaldehyde by humans, or (c) the effects of formaldehyde exposure may contribute in an additive or synergistic way to the effects of other carcinogens or tumor promoters.

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REFERENCES

1. Chemical Industry Institute of Toxicology. Statement concerning research findings, Docket #11109, October 8, 1979.
2. National Academy of Sciences. Formaldehyde—An assessment of its health effects. Committee on Toxicology, National Academy of Sciences, Washington, D.C., 1980.
3. Battelle Columbus Division. Final report on product/industry profile and related analysis for formaldehyde and formaldehyde-containing consumer products. CPSC-C-78-0091, Battelle, Columbus, Ohio, February 1979.
4. Urea-Formaldehyde Foam Insulation; Proposed Notice to Purchasers. Fed. Regist. 45 (113): 39434-39444 (1980).
5. Urea-Formaldehyde Foam Insulation; Public Hearings. Fed. Regist. 44 (233): 69578-69583 (1979).
6. Interagency Regulatory Liaison Group Meeting Report. Visit to CIIT, and Report of the IRLG Pathologists, Interagency Liaison Group, January 17-18, 1980.
7. Evaluation of Health Risks of Formaldehyde by Government Scientists. Fed. Regist. 45 (100): 34031-34033 (1980).
8. Kitchens, J. F., Casner, R. E., Edwards, G. S., Harward, W. E., and Macri, B. J. Investigation of Selected Potential Environmental Contaminants: Formaldehyde. U.S. Environmental Protection Agency, Washington, D.C., Report No. ARC-49-5681, 1976.
9. Egle, J. L. Retention of inhaled formaldehyde, propionaldehyde, and acrolein in the dog. Arch. Environ. Health 25: 119-124 (1972).
10. Malorny, G., Rietbrock, N., and Schneider, M. Die Oxydation des Formaldehyds zu Ameisensaeure im Blut, ein Beitrag zum Stoffwechsel des Formaldehyds. (Oxidation of formaldehyde to formic acid in blood, a contribution to the metabolism of formaldehyde.) Arch. Exptl. Pathol. Pharmakol. 250: 419-436 (1965).
11. Usdin, V. R., and Arnold, G. B. Transfer of formaldehyde to guinea pig skin. Gillette Research Inst. Report. Contract No. 78-391, 1979.
12. McMartin, K. E., Martin-Amat, G., Noker, P. E., and Tephly, T. R. Lack of role for formaldehyde in methanol poisoning in the monkey. Biochem. Pharmacol. 28: 645-649 (1979).
13. Rietbrock, N. Kinetik and Wege des Methanolumsatzes. (Kinetics and pathways of methanol metabolism). Arch. Exptl. Pathol. Pharmakol. 263: 88-105 (1969).
14. McMartin, K. E., Martin-Amat, G., Makar, A. B., and Tephly, T. R. Methanol poisoning V. Role of formate metabolism in the monkey. J. Pharmacol. Exptl. Therap. 201: 564-572 (1977).
15. Einbrodt, J. J., Prajsnar, D., and Erpenbeck, J. Der Formaldehyd und Ameisensaeurespiegel im Blut und Urin beim Menschen nach Formaldehyd-exposition. (Effect of formaldehyde exposure on people in school and living areas.) Zentralbl. Arbeitsmed. Arbeitsschutz Prophyl. 26 (8): 154-158 (1976).
16. Uotila, L., and Koivusalo, M. Formaldehyde dehydrogenase from human liver; purification, properties, and evidence for the formation of glutathione thiol esters by the enzyme. J. Biol. Chem. 249: 7653-7663 (1974).
17. Strittmatter, P., and Ball, E. G. Formaldehyde dehydrogenase, a glutathionine-dependent enzyme system. J. Biol. Chem. 213: 445-461 (1955).
18. Huennekens, F. M., and Osborn, M. J. Folic acid coenzymes and 1-carbon metabolism. Adv. Enzymol. 21: 369-446 (1959).
19. DuVigneaud, V., Verby, W. G., and Wilson, J. E. Incorporation of the carbon of formaldehyde and formate into the methyl groups of choline. J. Am. Chem. Soc. 72: 2819-2820 (1950).
20. Neely, W. B. The metabolic fate of formaldehyde-C^{14} intrapertitoneally administered to the rat. Biochem. Pharmacol. 13: 1137-1142 (1964).
21. Berg, P. Synthesis of labile methyl groups by guinea pig tissue in vitro. J. Biol. Chem. 190: 31-38 (1951).

22. Pruett, J. J., Scheuenstuhl, H., and Michaeli, D. L. The incorporation and localization of aldehydes (highly reactive cigarette smoke components) into cellular fractions of cultured human lung cells. Arch. Environ. Health 35: 15-20 (1980).
23. Waydhas, C., Weigl, K., and Sies, H. The disposition of formaldehyde and formate arising from drug N-demethylations dependent on cytochrome P-450 in hepatocytes and in perfused rat liver. Eur. J. Biochem. 89 (1): 143-150 (1978).
24. Palese, M., and Tephly, T. R. Metabolism of formate in the rat. J. Toxicol. Environ. Health 1: 13-24 (1975).
25. Aebi, H., and Roggen, G. Enzymatische Demethylierung von Dimethyl-C^{14}-aminoantipyrin. Pharm. Acta Helv. 33: 413-428 (1958).
26. Ahmed, A. E., and Anders, M. W. Metabolism of dihalomethanes to formaldehyde and inorganic halide-II. Studies on the mechanism of the reaction. Biochem. Pharmacol. 27: 20-21 (1978).
27. Laduron, P., and Leyson, J. Enzymatic formaldehyde production from 5-methyltetrahydrofolic acid: prior step to alkaloid formation. Biochem. Pharmacol. 24: 929-932 (1975).
28. Thorndike, J., and Beck, W. S. Production of formaldehyde from N5-methyltetrahydrofolate by normal and leukemic leukocytes. Cancer Res. 37: 1125-1132 (1977).
29. Gescher, A., Hickman, J. A., and Stevens, M. F. G. Oxidative metabolism of some N-methyl containing xenobiotics can lead to stable progenitors of formaldehyde. Biochem. Pharmacol. 28 (21): 3235-3238 (1979).
30. Goodman, J. I., and Tephly, T. R. A comparison of rat and human liver formaldehyde dehydrogenase. Biochem. Biophys. Acta 252: 489-505 (1971).
31. Den Engelse, L., Gebbink, M., and Emmelot, P. Studies on lung tumors. III. Oxidative metabolism of dimethylnitrosamine by rodent and human lung tissue. Chem. Biol. Interact. 11: 535-544 (1975).
32. Poverenny, A. M., Siomin Yu, A., Saenko, A. S., and Sinzinis, B. I. Possible mechanisms of lethal and mutagenic action of formaldehyde. Mutat. Res. 27: 123-126 (1975).
33. Goodman, L. S., and Gilman, A., Eds. The Pharmacological Basis of Therapeutics, 5th ed. Macmillan Publishing Co., New York., 1975, p. 1006.
34. Gofmekler, V. A. Effect on embryonic development of benzene and formaldehyde in inhalation experiments. Hyg. Sanit. (USSR) 33: 327-332 (1968).
35. Gofmekler, V. A., Pushkina, N. N., and Klevtsova, G. N. Some biochemical aspects of the embryotropic effect of benzene and formaldehyde. Hyg. Sanit. (USSR) 33: 112-116 (1968).
36. Pushkina, N. N., Gofmekler, V. A., and Kletsova, G. N. Changes in content of ascorbic acid and nucleic acids produced by benzene and formaldehyde. Bull. Exp. Biol. Med. 66: 868-870 (1968).
37. Gofmekler, V. A., and Bonashevskaya, T. I. Experimental studies of teratogenic properties of formaldehyde based on pathological investigations. Hyg. Sanit. (USSR) 34: 266-268 (1969).
38. Sheveleva, G. A. Investigation of the specific effect of formaldehyde on the embryogenesis and progeny of white rats. Toksikol. Novykh. Promysh. Khim. Veshchestv. 12: 78-86 (1971).
39. Guseva, V. A. Gonadotropic effects in male rats subjected to formaldehyde intake simultaneously via air and water. Hygiene Sanitation 10: 102-103 (1972).
40. Sanotskii, I. V., Fomenko, V. N., Sheveleva, G. A., Sal'nikova, L. S., Nakoryakova, M. V., and Pavlova, T. E. Effects of pregnancy on animal susceptibility to chemical agents. Gig. Tr. Prof. Zabol. No. 1: 25-28 (1976).
41. Hurni, G., and Ohder, H. Reproduction study with formaldehyde and hexamethylenetetramine in beagle dogs. Food Cosmet. Toxicol. 11: 459-462 (1973).
42. Natvig, H., Andersen, J., and Rasmussen, E. W. A contribution to the toxicological evaluation of hexamethylenetetramine. Food Cosmet. Toxicol. 9: 491-500 (1971).
43. Marks, T. A., Worthy, W. C., and Staples, R. E. Influence of formaldehyde and Sonacide (potentiated acid glutaraldehyde) on embryo and fetal development in mice. Teratology 22 (1): 51-58 (1980).
44. Della Porta, G., Cabral, F. R., and Parmiani, G. Studio della tossicita transplancentare e di cancerogenesi in ratti trattati con esametilentetramina. (Transpacental toxicity and carcinogenesis studies in rats with hexamethylenetetramine). Tumori 56: 325-334 (1970).
45. Shumilina, A. V. Menstrual and reproductive functions in workers with occupational exposure to formaldehyde. Gig. Tr. Prof. Zabol. No. 12: 18-21 (1975).
46. Palkovits, M., and Mitro, A. Morphological changes in the hypothalamopituitary-adrenal system during early postnatal period in rats. Gen. Comp. Endocrinol. 10: 253-262 (1968).
47. Cohen, A. Response of the adrenal glands in the rat fetus to formal injection during different stages of development. C. R. Acad. Sci. 275: 921-924 (1972).
48. Conner, E. A., Blake, D. A., Parmley, T. H., Burnett, L. S., and King, T. M. Efficacy of various locally applied chemicals as contragestational agents in rats. Contraception 13: 571-582 (1976).
49. Epstein, S. S., Arnold, E., Andrea, J., Bass, W., and Bishop, Y. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23: 288-325 (1972).
50. Auerbach, C., Moutschen-Dahmen, M., and Moutschen, J. Genetic and cytogenetical effect of formaldehyde and related compounds. Mutat. Res. 39: 317-362 (1977).
51. Cooper, P. Genetic effects of formaldehyde. Food Cosmet. Toxicol. 17: 300-301 (1979).
52. Rapoport, I. A. Carbonyl compounds and the chemical mechanism of mutations. Dokl. Akad Nauk SSSR 54: 65-67 (1946).
53. Kaplan, W. D. Formaldehyde as a mutagen in *Drosophila*. Science 108: 3 (1948).
54. Slizynska, H. Cytological analysis of formaldehyde induced chromosomal changes in *Drosophila melanogaster*. Proc. Roy. Soc. Edinb. B66: 288-304 (1957).
55. Auerbach, C. The mutagenic mode of action of formalin. Science 110: 419-420 (1949).
56. Demerec, M., Bertani, G., and Flint, J. A. A survey of chemicals for mutagenic action on *Escherichia coli*. Amer. Naturalist 85: 119-136 (1951).
57. Auerbach, C. Mutation tests on *Drosophila melanogaster* with aqueous solutions of formaldehyde. Amer. Naturalist 86: 330-332 (1952).
58. Sobels, F. H. Mutation tests with formaldehyde-hydrogen peroxide mixture in *Drosophila*. Amer. Naturalist 88: 109-112 (1954).
59. Brockman, H. E., de Serres, F. J., and Hung, C. Y. Mutagenicity of formaldehyde, NIH Contract Report, 1980.
60. Jensen, K. A., Kirk, I., Kolmark, G., and Westergaard, M. Chemically induced mutations in *Neurospora*. Cold Spring Harbor Symp. Quant. Biol. 16: 245-261 (1951).
61. Malling, H., Miltenburger, H., Westergaard, M., and Zimmer, K. G. Differential response of a double mutant—adenineless, inositolless—in *Neurospora crassa* to combined treatment by ultraviolet radiation and chemicals. Int. J. Radiat. Biol. 1: 328-343 (1959).
62. Nanda, G., Nandi, P., and Mishra, A. K. Studies on induced reversion at the arginine locus of *Aspergillus*

chevalieri (Mangin). Zentralbl. Bakteriol. Abt. II, 130: 105-108 (1975).
63. Koops, A., and Butterworth, B. E. *In vitro* microbial mutagenicity studies of formaldehyde (37% A.I.). E. I. DuPont de Nemours and Co., Haskell Laboratory Report No. 203-276, 1976.
64. Brusick, D. J., Jagannath, D., Myhr, B., and Stetka, D. The genetic activity of paraformaldehyde in the Ames assay, the L5178Y mouse lymphoma assay, the CHO SCE assay and an *in vitro* CHO chromosome analysis. Abstract of paper presented at the 11th Annual Meeting of the Environmental Mutagen Society, Nashville, Tenn., March 1980.
65. Gosser, L. B., and Butterworth, B. E. Mutagenicity evaluation of formaldehyde in the L5178Y mouse lymphoma assay. E. I. DuPont de Nemours and Co., Haskell Laboratory Report No. 581-580, 1977.
66. Obe, G., and Beek, B. Mutagenic activity of aldehydes. Drug Alcohol Depend. 4: 91-94 (1979).
67. Martin, C. N., McDermid, A. C., and Garner, R. C. Testing of known carcinogens and noncarcinogens for their ability to induce unscheduled DNA synthesis in HeLa Cells. Cancer Res. 38: 2621-2627 (1978).
68. Epstein, S. S., Arnold, E., Andrea, J., Bass, W., and Bishop, Y. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23: 288-325 (1972).
69. Sobels, F. H. Organic peroxides and mutagenic effects in *Drosophila*: Mutagenicity of dihydroxydimethylperoxide and the mutagenic effect of formaldehyde. Nature 177: 979-980 (1956).
70. Dickey, F. H., Cleland, G. H., and Lota, C. The role of organic peroxides in the induction of mutations. Proc. Natl. Acad. Sci. (U.S.) 35: 581-586 (1949).
71. Kolmark, G. Differential response to mutagens as studied by the *Neurospora* reverse mutation test. Hereditas 39: 270-276 (1953).
72. Kolmark, G., and Westergaard, M. Further studies on chemically induced reversions at the adenine locus of *Neurospora*. Hereditas 39: 209-224 (1953).
73. Nishioka, H. Lethal and mutagenic action of formaldehyde in HCR+ and HCR- strains of *Escherichia coli*. Mutat. Res. 17: 261-265 (1973).
74. Chanet, R., Izard, C., and Moustacchi, E. Genetic effects of formaldehyde in yeast. II. Influence of ploidy and of mutations affecting radiosensitivity of its lethal effect. Mutat. Res. 35: 29-38 (1976).
75. Magana-Schwencke, N., Ekert, B., and Moustacci, E. Biochemical analysis of damage in yeast by formaldehyde. I. Induction of single-strand breaks in DNA and their repair. Mutat. Res. 50: 181-193 (1978).
76. Fahrig, R. The mammalian spot test: A sensitive *in vivo* method for the detection of genetic alterations in somatic cells of mice. In: Chemical Mutagens: Principles and Methods for their Detection, Vol. 5, A. Hollaender, and F. J. de Serres, Eds., Plenum Press, New York, 1978, pp. 151-176.
77. Generoso, W. M., Cain, K. T., Huff, S. W., and Gosslee, D. G. Heritable translocation test in mice. In: Chemical Mutagens: Principles and Methods for their Detection, Vol. 5, A. Hollaender and F. J. de Serres, Eds., Plenum Press, New York, 1978, pp. 55-77.
78. Ehling, U. H. Specific locus mutations in mice. In: Chemical Mutagens: Principles and Methods for their Detection, Vol. 5, A. Hollaender and F. J. de Serres, Eds., Plenum Press, New York, 1978, pp. 233-256.
79. Swenberg, J. A., Kerns, W. D., Mitchell, R. J., Gralla, E. J., and Pavkov, K. L. Induction of squamous cell carcinoma of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res. 40: 3398-3402 (1980).
80. Chemical Industry Institute of Toxicology. Progress Report on CIIT Formaldehyde Studies, Docket No. 112DO, December 12, 1980.
81. Gralla, E. J., Heck, H. d'A., Hrubesh, L. W.,and Meadows, G. W. A report of the review of the formaldehyde exposure made by the CIIT ad hoc analytical chemistry investigative team held at the Battelle Memorial Columbus (Ohio) Laboratory. CIIT Docket #62620, January 11, 1980.
82. Laskin, S., Sellakumar, A. R., Kuschner, M., Nelson, N., LaMendola, S., Rush, G. M., Katz, G. V., Ehrlichman, M., Dulak, N. C., Snyder, C. A., and Albert, R. E. Nasal cancer in the rat induced by gaseous formaldehyde and hydrogen chloride. In press.
83. Kuschner, M., Laskin, S., Drew, R. T., Capiello, V., and Nelson, N. The inhalation carcinogenicity of alpha halo ethers. III. Lifetime and limited period inhalation studies with bis(chloromethyl) ether at 0.1 ppm. Arch. Environ. Health 30: 73-77 (1975).
84. Nettesheim, P. Respiratory carcinogenesis. Report of Progress in FY 1976 and 1977, NCI-DOE Cancer Research Program.
85. Horton, A. W., Tye, R., and Stemmer, K. L. Experimental carcinogenesis of the lung. Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. J. Natl. Cancer Inst. 30: 31-43 (1963).
86. Dalbey, W. E., and Nettesheim, P. (Oak Ridge National Laboratory, Oak Ridge, Tenn.). Personal communication, 1980.
87. Mueller, R., Raabe, G., and Schumann, D. Leukoplakia induced by repeated deposition of formalin in rabbit oral mucosa: Long-term experiments with a new "oral tank". Exptl. Pathol. 16: 36-42 (1978).
88. Brusick, D. J., Myhr, B. C., Stetka, D. G., and Rundell, J. O. Genetic and transforming activity of formaldehyde. Litton Bionetics Report, April 1980.
89. Watanabe, F., Matsunaga, T., Soejima, T., and Iwata, Y. Study on aldehyde carcinogenicity. Communication I. Experimentally induced rat sarcomas by repeated injection of formalin. Gann 45: 451-452 (1954).
90. Watanabe, F., and Sugimoto, S. Studies on the carcinogenicity of aldehydes. Part II. Seven cases of transplantable sarcomas of rats developed in the area of repeated subcutaneous injections of urotropin (hexamethylenetetramine). Gann 46: 365-367 (1955).
91. Brendel, R. Untersuchungen an Ratten zur Vertraeglichkeit von Hexamethylentetramin. (Hexamethylenetetramine tolerance in rats.) Arzneim. Forsch. 14: 51-53 (1964).
92. Della Porta, G., Colnaghi, M. I., and Parmiani, G. Noncarcinogenicity of hexamethylenetetramine in mice and rats. Food Cosmet. Toxicol. 6: 707-715 (1968).
93. Klenitzky, J. S. On experimental cancer of the uterine cervix. Bull. Biol. Med. Exp. 9: 3-6 (1940).
94. Feron, V. J., and Woutersen, B. A. Respiratory tract tumors in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene. Abstract of paper, Symposium on Cocarcinogenesis and Biological Effects of Tumor Promoters, sponsored by The German Cancer Research Center. Heidelberg, and IARC, Lyon, France, Elmau Castle, Klais, Bavaria, Germany, October 13-16, 1980.
95. Plugge, H., and Petrazzuolo, G. Nasal Oncogens-A Review. JRB Associates, Inc., Contract No. CPSC-C 79-1052, 1980.
96. Rusch, H. P. Extrinsic factors that influence carcinogenesis. Physiol. Rev. 44: 177-204 (1944).
97. Saffiotti, U., and Shubik, P. Studies on promoting action in skin carcinogenesis. Conference: Biology of Cutaneous Cancer NCI Monogr. No. 10: 489-507 (1963).
98. Raick, A. N., and Burdzy, K. Ultrastructural and biochem-

ical changes induced in mouse epidermis by a hyperplastic agent, ethylphenylpropiolate. Cancer Res. 33: 2221-2230 (1973).
99. Slaga, T. J., Bowen, G. T., and Boutwell, R. K. Acetic acid, a potent stimulator of mouse epidermal macromolecular synthesis and hyperplasia but with weak tumor-promoting ability. J. Natl. Cancer Inst. 55: 983-987 (1975).
100. Boutwell, R. K. Some biological aspects of skin carcinogenesis. Progr. Exp. Tumor Res. 4: 207-250 (1964).
101. Hennings, H., and Boutwell, R. K. Studies on the mechanisms of skin tumor promotion. Cancer. Res. 30: 312-320 (1970).
102. Argyris, T. S. Tumor promotion by damage induced epidermal hyperplasia in the skin of mice. Proc. Amer. Assoc. Cancer Res. 20: 4 (1979) (abstract); J. Invest. Dermatol. 75: 360-362 (1980).
103. Bertram, J. S., and Heidelberger, C. Cell cycle dependency of oncogenic transformation induced by *N*-methyl-*N'*-mitro-*N*-nitrosoguanidine in culture. Cancer Res. 34: 526-537 (1974).
104. Kakunaga, T. The role of cell division in the malignant transformation of mouse cells treated with 3-methylcholanthrene. Cancer Res. 35: 1637-1642 (1975).
105. Solt, D. B., and Farber, E. New principles for the analysis of chemical carcinogenesis. Nature 263: 701-703 (1976).
106. Boutwell, R. K. The function and mechanism of promoters of carcinogenesis. CRC Crit. Rev. Toxicol. 2: 419-443 (1974).
107. Hill, A. B. The environment and disease: association or causation? Proc. Roy. Soc. Med. (London) 58: 295-300 (1965).
108. National Institute of Occupational Safety and Health. NIOSH criteria for a recommended standard . . . occupational exposure to formaldehyde. DHEW (NIOSH) Publication No. 77-126, Washington, D.C., 1976.
109. Loomis, T. A. Formaldehyde toxicity. Arch. Pathol. Lab. Med., 103: 321-324 (1979).
110. National Academy of Sciences. Formaldehyde-An Assessment of Its Health Effects. Committee on Toxicology, National Academy of Sciences, Washington D.C. 1980.
111. Helander, I. Contact urticaria from leather containing formaldehyde. Arch. Dermatol. 113: 1433 (1977).
112. Harris, D. K. Health problems in the manufacture and use of plastics. Brit. J. Ind. Med. 10: 255-268 (1953).
113. Sakula, A. Formalin asthma in hospital laboratory staff. Lancet (7939): 816 (1975).
114. Porter, J. A. H. Acute respiratory distress following formalin inhalation. Lancet (7935): 603-604 (1975).
115. Rader, J. Irritative effects of formaldehyde in laboratory halls. Analytical and experimental investigations. Dissertation, Institute for Pharmacology and Toxicology of the University of Wuerzburg, 1974.
116. Breysse, P. A. Formaldehyde in mobile and conventional homes. Environ. Health Saf. News 26 (1-6): 20 pp. (1977).
117. Schuck, E. A., Stephens, E. R., and Middleton, J. T. Eye irritation response at low concentrations of irritants. Arch. Environ. Health 13: 570-575 (1966).
118. Garry, V. F., Oatman, L., Pleus, R., and Gray, D. Minnesota Department of Health. Formaldehyde in the home. Some environmental disease perspectives. Minn. Med. 63: 107-111 (1980).
119. Sardinas, A. V.,Most, R. S., Guilietti, M. A., and Honchar, P. Health effects associated with urea-formaldehyde foam insulation in Connecticut. J. Environ. Health 41: 270-272 (1979).
120. Schoenberg, J. A., and Mitchell, C. A. Airway disease caused by phenolic (phenol-formaldehyde) resin exposure. Arch. Environ. Health 30: 574-577 (1975).
121. Kerfoot, E. J., and Mooney, T. F. Formaldehyde and paraformaldehyde study in funeral homes. Am. Ind. Hyg. Assoc. J. 36: 533-537 (1975).
122. Orringer, E. P. and Mattern, W. D. Formaldehyde-induced hemolysis during chronic hemodialysis. New Engl. J. Med. 294: 1416-1420 (1976).
123. Weber-Tschopp, A., Fischer, T., and Grandjean, E. Irritating effects of formaldehyde on men. Int. Arch. Occup. Environ. Health 39: 207-218 (1977).
124. Fassett, D. W. Aldehydes and acetals. In: Industrial Hygiene and Toxicology. 2nd rev. ed., Vol. 11, F. A. Patty, Ed., Interscience, New York. 1963, pp. 1959-1989.
125. Gamble, J. F., McMichael, A. J., Williams, T., and Battigelli, M. Respiratory function and symptoms: An environmental-epidemiological study of rubber workers exposed to phenol-formaldehyde type resin. Am. Ind. Hyg. Assoc. J. 37: 499-513 (1976).
126. Hendrick, D. J., and Lane, D. J. Occupational formalin asthma. Brit. J. Ind. Med. 34: 11-18 (1977).
127. Yefremov, G. G. The upper-respiratory tract in formaldehyde production workers (results of a special investigation). Zh. Ushn. Nos. Gore. Bolezn. 30: 11-15 (1970).
128. Kratochvil, I. Effects of formaldehyde on the health of workers in the crease-resistant clothing industry. Pracovni Lekarstvi, 23: 374-375 (1971).
129. Shumilina, A. V. Menstrual and reproductive functions in workers with occupational exposure to formaldehyde. Gig. Tr. Prof. Zabol. 12: 18-21 (1975).
130. Neshkov, N. S., and Nosko, A. M. Effect of toxic components of fiberglass-reinforced plastics on the higher nervous activity and sexual function in male workers. Gig. Tr. Prof. Zabol. 12: 92-94 (1976).
131. Cooper, E. R. A., Jones, A. R., and Jackson, H. Effects of alpha-chlorohydrin and related compounds on the reproductive organ and fertility of the male rats. J. Reprod. Fertil. 38: 379 (1974).
132. Jones, A. R., Davis, P., Edwards, K., and Jackson, H. Antifertility effects and metabolism of alpha and epichlorohydrins in the rat. Nature 244: 83 (1969).
133. Ishchenko, U. N., and Pushkina, I. K. Evaluation of working conditions in a plant engaged in processing phenol formaldehyde resins. Gig. Sanit. 11: 98-100 (1978).
134. Plunkett, E. R., and Barbela, T. Are embalmers at risk? Am. Ind. Hyg. Assoc. J. 38: 61-62 (1977).
135. Engel, H. O., and Calnan, C. D. Resin dermatitis in a car factory. Brit. J. Ind. Med. 23: 62-66 (1966).
136. Schwartz, L., Peck, S. M., and Dunn, J. E. Dermatitis from resin glue in war industries. Public Health Repts. 58: 899-904 (1943).
137. Sneddon, I. B. Dermatitis in an intermittent haemodialysis unit. Brit Med. J. 1: 183-184 (1968).
138. Moss, E. and Lee, W. R. Occurrence of oral and pharyngeal cancer in textile workers. Brit. J. Ind. Med. 31: 224-232 (1974).
139. Bross, I. D. J., Viadama, E., and Houten, L. Occupational cancer in men exposed to dust and other environmental hazards. Arch. Environ. Health 33: 300-307 (1978).
140. Decoufle, P. Cancer risk associated with employment in leather products industry. Arch. Environ. Health 34: 33-37 (1979).
141. Fajen, J. M. Industrial hygiene aspect of the carcinogenic risk for humans in leather tanneries. Unpublished report, 1980, prepared for IARC monograph, No. 25, 1981.
142. Matanoski, J. Data presented at the 49th meeting of the Interagency Collaborative Group on Environmental Carcinogenesis. Bethesda, Md., February 6, 1980.
143. Crump, K. S., Guess, H. A., and Deal, K. L. Confidence intervals and tests of hypotheses concerning dose response relations inferred from animal carcinogenicity data. Biometrics 33: 437-451 (1977).